UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

February 24, 2015

SUBJECT: **Difenoconazole:** Human Health Risk Assessment for proposed new foliar uses on legume subgroup 6C and bushberry subgroup 13-07B; post-harvest uses on pome fruit group 11-10; and ornamental plants and vegetable transplants grown in both indoor and outdoor production facilities.

PC Code: 128847

Decision Nos.: 486674, 484399, 486689, 486690, 486686, 486687, 479716

Petition Nos.: 3F8209, 4F8231
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcodes: D422992, D421429, D421216, D421201, D421208, D421188, D413471
Registration Nos.: 100-RLEO (EPA File Symbol), 100-RLNA (EPA File Symbol); 100-739, 100-1262, 100-1312, 100-1313, 100-1317
Regulatory Action: Section 3 Registration
Case No.: 7014
CAS No.: 119446-68-3
40 CFR: §180.475

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This document provides the Health Effects Division's (HED's) risk assessment of proposed new foliar uses on legume subgroup 6C and bushberry subgroup 13-07B; and new end-use products for new uses for post-harvest applications on pome fruit group 11-10 and to control fungal diseases on ornamental plants and vegetable transplants.

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1.0 EXECUTIVE SUMMARY

This document provides the Health Effects Division's (HED's) risk assessment of proposed new foliar uses on pea and bean, dried shelled, except soybean, subgroup 6C and bushberry subgroup 13-07B; new end-use product (EPA File Symbol 100-RLEO) for new post-harvest uses on pome fruit 11-10; and new end-use product (EPA File Symbol 100-RLNA) for new use to control fungal diseases on ornamental plants and vegetable transplants grown in both indoor and outdoor production facilities. It also assesses potential enhanced sensitivity of infants and children from dietary and/or residential exposure as required under the Food Quality Protection Act (FQPA) of 1996.

Use Profile

Difenoconazole is a broad spectrum fungicide belonging to the triazole group of fungicides. It is currently registered in the U.S. for use as a seed treatment on a number of cereal grain crops, cotton, potato seed pieces and canola and for foliar application to numerous food crops and ornamentals and for post-harvest use on tuberous and corm vegetables subgroup 1C. Tolerances for difenoconazole, currently established under 40 CFR §180.475, range from 0.01-95 ppm. Difenoconazole acts by blocking demethylation during sterol biosynthesis which, in turn, disrupts membrane synthesis. Difenoconazole is available as emulsifiable concentrate, soluble concentrate, emulsion [oil] in water, flowable suspension, and ready-to-use formulations. As a seed treatment, it is applied with commercial grade seed treatment equipment. As a foliar treatment, it is applied to field and vegetable crops, landscape ornamentals and golf course turf by commercial applicators using aerial and ground application methods and equipment. It is applied to ornamentals by residential applicators using hand held sprayers.

Proposed New Uses

In conjunction with PP#3F8209, Syngenta is requesting registration of a new multiple active ingredient (MAI) end-use product, Academy™ Fungicide (EPA File Symbol 100-RLEO), formulated as a flowable suspension concentrate (SC) containing both difenoconazole (20.9%; 2.06 lb ai/gal) and fludioxonil (12.5%; 1.23 lb ai/gal), for new post-harvest dip, drench, flood or spray uses of difenoconazole on pome fruit group 11-10. A single post-harvest application is proposed at 0.26 lb ai/100 gal for dip, drench or flood treatments and 0.26 lb ai/200,000 lb of fruit for spray treatment.

In conjunction with PP#4F8231, Syngenta is proposing an amended Section 3 registration for a 2.08 lb ai/gal emulsifiable concentrate (EC) formulation (Inspire™ Fungicide; EPA Reg. No. 100-1262) to add uses on members of pea and bean, dried shelled, except soybean, subgroup 6C and bushberry subgroup 13-07B. In addition, Syngenta is proposing to add some or all of the proposed uses to the following multiple active ingredient (MAI) products: a 2.08 lb ai/gal MAI EC formulation with propiconazole (Inspire™ XT Fungicide; EPA Reg. No. 100-1312); a 1.05 lb ai/gal MAI suspension concentrate (SC) formulation with azoxystrobin (Quadris Top™ Fungicide; EPA Reg. No. 100-1313); and a 0.73 lb ai/gal MAI emulsion oil in water (EW) formulation with cyprodinil (Inspire Super ™ Fungicide; EPA Reg. No. 100-1317). The proposed uses are for multiple foliar applications at up to 0.115 lb ai/A/application for maximum

seasonal rates of 0.46 lb ai/A on dried peas (EPA Reg Nos. 100-1262 and 100-1313 only), dried beans and bushberries with a 7-day minimum retreatment interval (RTI) and pre-harvest intervals (PHIs) of 14-days for dried peas/beans and 7-days for bushberries. [Note: Because there are no currently established tolerances for residues of propiconazole and cyprodinil in/on dried peas, Syngenta is not proposing use of Inspire™ XT Fungicide (EPA Reg. No. 100-1312) and Inspire Super™ Fungicide (EPA Reg. No. 100-1317) on dried peas.]

Syngenta is requesting registration of a new MAI end-use product, Alibi Flora™ (EPA File Symbol 100-RLNA), formulated as a flowable suspension concentrate (SC) containing both difenoconazole (11.4%; 1.05 lb ai/gal) and azoxystrobin (18.2%; 1.67 lb ai/gal) which is identical in composition to already registered products Quadris Top™ (EPA Reg. No. 100-1313) and Briskway™ (EPA Reg. No. 100-1433). Alibi Flora™ (EPA File Symbol 100-RLNA) is proposed for new uses to control diseases in ornamentals and a variety of vegetable transplants produced for sale to residential consumers only, grown in greenhouses, shade houses, lath houses, other outdoor growing structures and outdoor nurseries. Alibi Flora™ (EPA File Symbol 100-RLNA) is proposed for use at a maximum single application rate (maximum total rate) of 0.13 lb ai/A/application (0.52 lb ai/A) to ornamental plants; 0.113-0.115 lb ai/A/application (0.45-0.46 lb ai/A) to *Brassica* Cole Leafy Vegetable transplants, dry bulb onion transplants, cucurbit vegetable transplants and fruiting vegetable (except tomato) transplants; 0.115 lb ai/A/application (0.34 lb ai/A) to green onion transplants; and 0.07 lb ai/A/application (0.39 lb ai/A) to tomato transplants. No new residue chemistry data were submitted with this request; however, difenoconazole formulated as an SC (i.e., Quadris Top™ (EPA Reg. No. 100-1313)) is already registered for use on these same vegetables at the proposed maximum use rates for Alibi Flora™ (EPA File Symbol 100-RLNA) but for late-season foliar applications and short PHIs (0- to 7-days). Hence, existing tolerances will cover the requested new vegetable transplant uses of the Alibi Flora™ (EPA File Symbol 100-RLNA).

This review addresses difenoconazole only. Other active ingredients and uses listed on the new end-use product labels will not be discussed herein.

Toxicological Effects

The toxicology database for difenoconazole is complete for evaluating and characterizing toxicity and selecting endpoints for purposes of this risk assessment. Subchronic and chronic toxicity studies with difenoconazole in mice and rats showed decreased body weights and effects on the liver (e.g. hepatocellular hypertrophy, liver necrosis, fatty changes in the liver). Acute and subchronic neurotoxicity studies showed evidence of neurotoxic effects. However, the observed effects were transient and the dose-response was well characterized with identified dose levels at which no observed adverse effects were seen. The available developmental and reproduction toxicity studies indicated no increased susceptibility of rats or rabbits from *in utero* or postnatal exposure to difenoconazole. In an immunotoxicity study in mice, difenoconazole produced immunotoxicity at doses that caused systemic toxicity. No evidence of carcinogenicity was seen in the chronic/cancer rat study. Evidence for carcinogenicity was seen in mice as induction of liver tumors at doses which were considered to be excessively high for carcinogenicity testing. Difenoconazole has been classified as "Suggestive Evidence of Carcinogenic Potential" with risk quantified using a non-linear (Margin of Exposure) approach (TXR 0054532). The cancer

classification is based on excessive toxicity observed at the two highest doses, the absence of tumors at the lower doses and the absence of genotoxic effects. The FQPA Safety Factor is reduced to 1X. Difenoconazole exhibits low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not an eye or skin irritant and is not a sensitizer.

Dose Response Assessment

Toxicological points of departure (PODs) were selected for dietary and drinking water exposures for the assessment of proposed new uses of difenoconazole. Acute and chronic PODs were selected for assessment of food and water exposures. An acute POD for all populations was selected from an acute neurotoxicity study in rats based on reduced grip strength. A chronic POD was selected from a chronic/carcinogenicity study in rats based on body weight effects. Short and intermediate-term incidental oral, dermal and inhalation PODs were selected from an oral rat reproduction study based on decreased body weight effects in pups and parental animals. A dermal absorption factor is applied when dermal exposure endpoints are selected from oral toxicity studies. A dermal absorption factor of 6%, based on triple pack data, was used for the dermal exposure assessment. Inhalation toxicity is assumed to be equivalent to oral toxicity. An uncertainty factor of 100X was applied endpoints selected for all exposures routes (10X for interspecies extrapolation, 10X for intraspecies variation, 1X FQPA SF).

Exposure/Risk Assessment and Risk Characterization

Conservative acute and refined chronic dietary and drinking water risk assessments for difenoconazole conclude that dietary and drinking water exposure estimates are below HED's level of concern for the general population and all population subgroups. At the 95th percentile, the exposure to the general U.S. population is 15% of the aPAD; the highest exposed subgroup (All Infants < 1 yr) is 49% of the aPAD. The exposure to the general U.S. population is 26 % of the cPAD, and the most highly exposed subgroup (Children 1-2 yrs old) is 88 % of the cPAD. The addition of the new uses did not increase the dietary exposure assessment for triazole Therefore, the triazole dietary exposure assessment did not require updating. A new residential assessment was not performed because, even though potential exposure from proposed uses on ornamental plants was identified, these uses were previously assessed at the same rate in a recent memo (D412811, I. Nieves, 11/13/2013). No residential risk estimates of concern were identified. Previously assessed residential exposure risk estimates were combined with current dietary exposure estimates for the aggregate risk assessment. Aggregate risk estimates were not of concern. Risk estimates for occupational handler and post-application exposure scenarios for most proposed uses have been also previously assessed at a similar and/or higher rate than the proposed uses (D398608, I. Nieves, 05/30/2012; D412811, I. Nieves, 11/13/2013) and therefore are not of concern at maximum use rates for existing and proposed new uses. The proposed use on ornamentals, was previously assessed in 2011 (D371037, B. Daiss, 2/24/11), at a higher application rate than currently proposed (0.003 lb ai/gal vs. 0.0011lbai/gal). However, to reflect recent updates (2012) to HED's occupational exposure SOPs and body weight assumptions, it was reassessed based on the proposed use pattern and no risk estimates of concern were identified for occupational handlers nor post-application activities.

Aggregate Assessment of Free Triazole & its Conjugates

The addition of the new uses does not increase the aggregate exposure to free triazoles and its conjugates. The aggregate human health risk assessment was previously updated for free triazoles and its conjugates and the aggregate estimates remain below HED's level of concern (T. Morton, D414952, 10/24/13).

Use of Human Studies

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, listed in Appendix 2.0, have been determined to require a review of their ethical conduct. Some of these studies are also subject to review by the Human Studies Review Board. All of the studies used have received the appropriate review.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Tolerance Recommendation

Pending submission of a revised Section F (see requirements under Sections 2.2.3 and 2.2.4 below) of petition 3F8209, HED has no objection to the registration of the new end-use product, Academy™ Fungicide (EPA File Symbol 100-RLEO), for the proposed post-harvest uses on pome fruit group 11-10 or increasing the established tolerances for residues of difenoconazole in/on the following:

Fruit, pome, group 11-10	from 1.0 ppm to 5.0 ppm
Apple, wet pomace	from 4.5 ppm to 25 ppm

Pending submission of a revised Section F (see requirements under Sections 2.2.3 and 2.2.4 below) and Section B (see requirements under Section 2.3 below) of petition 4F8231, HED has no objections to granting the proposed foliar uses on pea and bean, dried shelled, except soybean, subgroup 6C and bushberry subgroup 13-07B or establishment of tolerances for residues of difenoconazole in/on the following:

Pea and bean, dried shelled, except soybean, subgroup 6C.....0.20 ppm
Pea, field, hay .....40 ppm
Pea, field, vines.....10 ppm
Bushberry subgroup 13-07B.....4.0 ppm

The recommended tolerances for residues of difenoconazole in/on fruit, pome, group 11-10 and apple, wet pomace (5.0 ppm and 25 ppm, respectively) are not the same as the petitioned-for tolerances (3.0 ppm and 7.5 ppm, respectively). The recommended tolerance for residues of difenoconazole in/on bushberry subgroup 13-07B (4.0 ppm) is not the same as the petitioned-for tolerance (3.0 ppm) due to the independent field trial determination. The petitioned-for tolerance for residues of difenoconazole in/on pea and bean, dried shelled, except soybean, subgroup 6C tolerance (0.2 ppm) must be corrected to 0.20 ppm, consistent with current practices for setting tolerances. Although not petitioned-for, the currently established tolerance for residues of difenoconazole and its metabolite CGA-205375, expressed as difenoconazole equivalents, in milk should be increased from 0.01 ppm to 0.02 ppm and, with the establishment of a tolerance in/on pea and bean, dried shelled, except soybean, subgroup 6C (0.20 ppm), the currently established tolerance for residues of difenoconazole in/on chickpea (0.08 ppm) should be deleted. There are also some minor changes needed to the commodity definitions. See Table 1 for details.

Table 1. Tolerance Summary for Difenoconazole.

Commodity	**Petitioned-for Tolerance (ppm)**	**Recommended Tolerance (ppm)**	***Correct Commodity Definition;* Comments**
Bushberry, subgroup 13-07B	3.0	4.0	*Bushberry subgroup 13-07B*
Pea and bean, dried shelled (except soybean), subgroup 6C	0.2	0.20	*Pea and bean, dried shelled, except soybean, subgroup 6C*
Peas, hay	40	40	*Pea, field, hay*
Peas, vines	10	10	*Pea, field, vines*
Chickpea	Currently established at 0.08	delete	With the establishment of a tolerance in/on pea and bean, dried shelled, except soybean, subgroup 6C (0.20 ppm), the currently established tolerance in/on chickpea (0.08 ppm) is not appropriate and should be deleted.

Table 1. Tolerance Summary for Difenoconazole.			
Commodity	**Petitioned-for Tolerance (ppm)**	**Recommended Tolerance (ppm)**	***Correct Commodity Definition;* Comments**
Milk	Currently established at 0.01	0.02	The new dried pea hay and vine feedstuffs significantly increased the maximum reasonably balance diet (MRBD) for dairy cattle (from 2.8 ppm to 7.2 ppm). Based on the MRBDs for livestock and the available feeding study data, HED concludes that the currently established tolerance for residues of difenoconazole and its metabolite CGA-205375, expressed as difenoconazole equivalents, in milk should be increased from 0.01 ppm to 0.02 ppm to support the proposed new uses on dried peas. Other currently established livestock commodity tolerances remain adequate.
Fruit, pome, group 11-10	3.0	5.0	*Pome fruit group 11-10*
Apple, pomace, wet	7.5	25	*Apple, pomace, wet*

A Codex maximum residue limit (MRL) for residues of difenoconazole in/on pome fruit is proposed at 0.8 mg/kg based on data reflecting foliar applications of difenoconazole. The Codex MRL would not be adequate to cover residues incurred from the proposed post-harvest uses in the U.S.; therefore, harmonization with Codex is not possible at this time. A Mexican MRL has not been established for the requested crops. A Canadian MRL is established at 1 mg/kg in/on members of pome fruit group 11-10 (listed as individual crops); however, the submitted apple and pear magnitude of the residue data were evaluated under a joint review agreement between Health Canada's Pest Management Regulatory Agency (PMRA) and the USEPA and PMRA is expected to revise its MRL to harmonize with the U.S. recommended tolerance (5.0 ppm) at the end of their review.

Codex maximum residue limits (MRLs) are not established for residues of difenoconazole in/on members of the pea and bean, dried shelled, except soybean, subgroup 6C and harmonization with the established Canadian MRLs in/on a variety dried pea seeds and dried bean seeds (all at 0.03 ppm) is not possible because the Canadian MRL would not be adequate to cover residues expected from the proposed foliar uses in the U.S. There are no established Codex, Canadian or Mexican MRLs for residues of difenoconazole in/on members of the bushberry subgroup 13-07B, pea hay and pea vines so harmonization is not possible. For milk, the residue definition (sum of parent and its metabolite, CGA-205375) and recommended milk tolerance increase (from 0.01 ppm to 0.02 ppm) will harmonize with the established Codex MRL in milk but not the established Canadian MRL (0.01 ppm) which is limited to residues of parent only.

2.0 HED RECOMMENDATIONS

2.1 Data Deficiencies

Pending further amendments to the proposed uses on pea and bean, except soybean, subgroup 6C (See requirements under Section 2.3 Label Recommendations), HED can recommend for registration and permanent tolerances for the proposed uses of difenoconazole. Deficiencies are stated below. The specific tolerance recommendations are discussed in Section 2.2.3 Recommended Tolerances.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

An adequate enforcement method, GC/NPD method AG-575B, is available for the determination of residues of difenoconazole *per se* in/on plant commodities. An adequate enforcement method, LC/MS/MS method REM 147.07b, is available for the determination of residues of difenoconazole and CGA-205375 in livestock commodities. Adequate confirmatory methods are also available.

2.2.2 Recommended Tolerances

Pending submission of a revised Section F (see requirements under Sections 2.2.3 and 2.2.4) of petition 3F8209, HED has no objection to the registration of the new end-use product, Academy™ Fungicide (EPA File Symbol 100-RLEO), for the proposed post-harvest uses on pome fruit group 11-10 or increasing the established tolerances for residues of difenoconazole in/on the following:

Fruit, pome, group 11-10 .....from 1.0 ppm to 5.0 ppm
Apple, wet pomace .....from 4.5 ppm to 25 ppm

Pending submission of a revised Section F (see requirements under Sections 2.2.3 and 2.2.4) and Section B (see requirements under Section 2.3) of petition 4F8231, HED has no objections to granting the proposed foliar uses on pea and bean, dried shelled, except soybean, subgroup 6C and bushberry subgroup 13-07B or establishment of tolerances for residues of difenoconazole in/on the following:

Pea and bean, dried shelled, except soybean, subgroup 6C.....0.20 ppm
Pea, field, hay .....40 ppm
Pea, field, vines.....10 ppm
Bushberry subgroup 13-07B.....4.0 ppm

Although not petitioned-for, with the establishment of a tolerance in/on pea and bean, dried shelled, except soybean, subgroup 6C (0.20 ppm), the currently established tolerance for residues of difenoconazole in/on chickpea (0.08 ppm) should be deleted.

Although not petitioned-for, the currently established tolerance for residues of difenoconazole and its metabolite CGA-205375, expressed as difenoconazole equivalents, in milk should be increased from 0.01 ppm to 0.02 ppm. The new pea hay and vine feedstuffs significantly increased the dietary burden calculation for dairy cattle. Based on the re-calculated livestock dietary burdens and available feeding study data, HED concludes that the milk tolerance needs to be increased. Other currently established livestock commodity tolerances remain adequate.

The Organization for Economic Cooperation and Development tolerance calculation procedures were utilized in determining the appropriate tolerance level for the proposed uses. The proposed and recommended tolerances for residues of difenoconazole as a result of the subject action are presented in Table 2.2.3.

Table 2.2.2. Tolerance Summary for Difenoconazole.

Commodity	**Petitioned-for Tolerance (ppm)**	**Recommended Tolerance (ppm)**	***Correct Commodity Definition;* Comments**
Bushberry, subgroup 13-07B	3.0	4.0	*Bushberry subgroup 13-07B*
Pea and bean, dried shelled (except soybean), subgroup 6C	0.2	0.20	*Pea and bean, dried shelled, except soybean, subgroup 6C*
Peas, hay	40	40	*Pea, field, hay*
Peas, vines	10	10	*Pea, field, vines*
Chickpea	Currently established at 0.08	delete	With the establishment of a tolerance in/on pea and bean, dried shelled, except soybean, subgroup 6C (0.20 ppm), the currently established tolerance in/on chickpea (0.08 ppm) is not appropriate and should be deleted.
Milk	Currently established at 0.01	0.02	The new dried pea hay and vine feedstuffs significantly increased the maximum reasonably balance diet (MRBD) for dairy cattle (from 2.8 ppm to 7.2 ppm). Based on the MRBDs for livestock and the available feeding study data, HED concludes that the currently established tolerance for residues of difenoconazole and its metabolite CGA-205375, expressed as difenoconazole equivalents, in milk should be increased from 0.01 ppm to 0.02 ppm to support the proposed new uses on dried peas. Other currently established livestock commodity tolerances remain adequate.
Fruit, pome, group 11-10	3.0	5.0	*Fruit, pome, group 11-10*
Apple, pomace, wet	7.5	25	*Apple, wet pomace*

2.2.3 Revisions to Petitioned-For Tolerances

The recommended tolerance for residues of difenoconazole in/on bushberry, subgroup 13-07B (4.0 ppm) is not the same as the petitioned-for tolerance (3.0 ppm) due to the independent field trial determination which resulted in the exclusion of one of the trials from the OCED tolerance calculation procedures. The recommended pea and bean, dried shelled, except soybean, subgroup 6C tolerance of 0.20 ppm is based on the current practice of setting tolerances to 2 significant figures. Although not petitioned-for, the currently established tolerance in/on chickpea (0.08 ppm) should be deleted. Also, although not petitioned-for, because of the new pea hay and vine feedstuffs which significantly increased the maximum reasonably balanced dietary estimate for dairy cattle, the currently established tolerance in milk will need to be increased from 0.01 ppm to 0.02 ppm.

The recommended tolerances for residues of difenoconazole in/on fruit, pome, group 11-10 and apple, wet pomace (5.0 ppm and 25 ppm, respectively) are not the same as the petitioned-for tolerances (3.0 ppm and 7.5 ppm, respectively) which are deemed too low to cover difenoconazole residues which might be incurred from the proposed post-harvest use rates and techniques. Although both Syngenta and HED have used the OECD calculation procedures to determine tolerance levels in/on fruit, pome, group 11-10, Syngenta's petitioned-for tolerance level is based on the combined residue data for both representative commodities (i.e., apples and pears) and some of the post-harvest application techniques but not all (i.e., dip and drench but not spray or dip+spray). However, HED, consistent with current practices, calculated separate tolerance levels for each representative commodity paired with each of the different post-harvest application techniques and then selected the maximum tolerance estimate from these combinations as the recommended tolerance level. Furthermore, PMRA is expected to use this same approach and revise its MRL in/on members of pome fruit group 11-10 to harmonize with the U.S. recommended tolerance (5.0 ppm) at the end of their review.

Syngenta did not provide any explanation for the petitioned-for level in apple, wet pomace. However, HED, consistent with current practices, calculated the recommended tolerance based on the highest average field trial (HAFT) residues in/on apple (2.59 ppm) and the average processing factor for wet pomace (9.5x).

2.2.4 International Harmonization

A Codex maximum residue limit (MRL) for residues of difenoconazole in/on pome fruit is proposed at 0.8 mg/kg based on data reflecting foliar applications of difenoconazole. The Codex MRL would not be adequate to cover residues incurred from the proposed post-harvest uses in the U.S.; therefore, harmonization with Codex is not possible at this time. A Mexican MRL has not been established for the requested crops. A Canadian MRL is established at 1 mg/kg in/on members of pome fruit group 11-10 (listed as individual crops); however, the submitted apple and pear magnitude of the residue data were evaluated under a joint review agreement between Health Canada's Pest Management Regulatory Agency (PMRA) and the USEPA and PMRA is expected to revise its MRL to harmonize with the U.S. recommended tolerance (5.0 ppm) at the end of their review.

Codex maximum residue limits (MRLs) are not established for residues of difenoconazole in/on members of the pea and bean, dried shelled, except soybean, subgroup 6C and harmonization with the established Canadian MRLs in/on a variety dried pea seeds and dried bean seeds (all at 0.03 ppm) is not possible because the Canadian MRL would not be adequate to cover residues expected from the proposed foliar uses in the U.S. There are no established Codex, Canadian or Mexican MRLs for residues of difenoconazole in/on members of the bushberry subgroup 13-07B, pea hay and pea vines so harmonization is not possible. For milk, the residue definition (sum of parent and its metabolite, CGA-205375) and recommended milk tolerance increase (from 0.01 ppm to 0.02 ppm) will harmonize with the established Codex MRL in milk but not the established Canadian MRL (0.01 ppm) which is limited to residues of parent only.

Note to the PM: Syngenta submitted eleven blueberry field trials conducted in Canada and the United States to support the proposed use of difenoconazole on members of bushberry subgroup 13-07B. However, an analysis of the field trials found that two of the trials conducted in Canada and representing NAFTA Growing Region 1 (Trials T162 and T163) were not independent according to criteria agreed to by EPA and Health Canada's Pesticide Management Regulatory Authority (PMRA) (i.e., Replicate trial guidance presented in draft memo 568_Criteria for Independence of Trials 04/23/2013). Hence, only three independent field trials were conducted in NAFTA Growing Region 1 (PE and NS; 3 trials). While this finding was not a deficiency for EPA which only requires 1 blueberry field trial from NAFTA Growing Region 1, it could be a deficiency for PMRA which requires 4 blueberry field trials from NAFTA Growing Region 1. Furthermore, since the present action is not being conducted as a joint review with PMRA and there is no indication that the subject data are under review by PMRA, HED cannot coordinate with PMRA regarding harmonization of the bushberry subgroup 13-07B tolerance level.

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

The recommended amendments to the directions for use on pea and bean, except soybean, subgroup 6C are presented below in relation to the submitted draft supplemental labels for Inspire™ Fungicide (EPA Reg. No. 100-1262; draft dated 10/2/14), Inspire™ XT Fungicide (EPA Reg. No. 100-1312; draft dated 10/2/14), Quadris Top™ Fungicide (EPA Reg. No. 100-1313; draft dated 10/2/14) and Inspire Super ™ Fungicide (EPA Reg. No. 100-1317; draft dated 10/10/14). However, Section B of petition 4F8231 should also be amended, as needed, to be consistent with the final version of the directions for use on the amended labels, including the plant-back intervals (PBI) which were specified on the supplemental labels but not in Section B of the petition.

- The proposed labels for Inspire™ Fungicide (EPA Reg. No. 100-1262; draft dated 10/2/14) and Quadris Top™ Fungicide (EPA Reg. No. 100-1313; draft dated 10/2/14) should be amended to specify a total maximum use rate of 0.23 lb ai/A on pea vines and hay consistent with the supporting field trial data.
- The proposed labels for Inspire™ Fungicide (EPA Reg. No. 100-1262; draft dated 10/2/14), Inspire™ XT Fungicide (EPA Reg. No. 100-1312; draft dated 10/2/14), Quadris Top™ Fungicide (EPA Reg. No. 100-1313; draft dated 10/2/14) and Inspire Super ™ Fungicide (EPA Reg. No. 100-1317; draft dated 10/10/14) should be amended to

specify a 14-day minimum retreatment interval for uses on members of pea and bean, dried shelled, except soybeans, subgroup 13-07B consistent with the supporting field trial data. In the absence of supporting cowpea hay and forage field trial data, these proposed labels must also be amended to include the following restriction for uses on dried beans: "To be grown for bean, dried seed only. Do not feed or harvest cowpea forage and hay." An unqualified restriction on the use of difenoconazole on cowpea is <u>not</u> required since cowpea seed may be harvested.

3.0 INGREDIENT PROFILE

3.1 Chemical Identity

Structure and nomenclature are reported in Table 3.1.

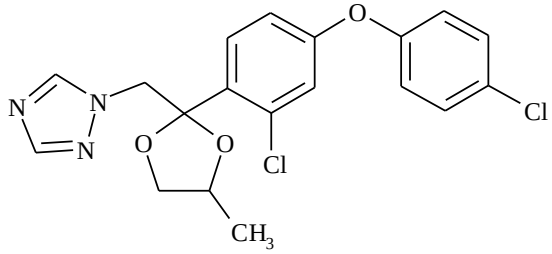
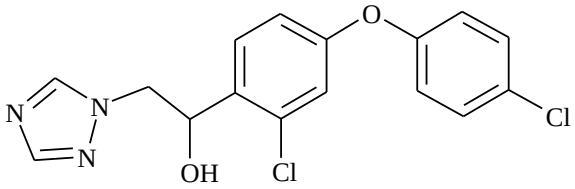
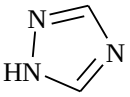
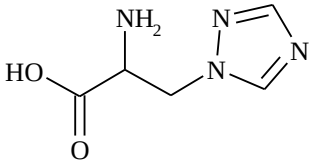
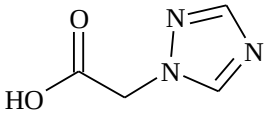
Table 3.1. Difenoconazole Nomenclature.	
Chemical structure of parent	 mol. wt. 406.3
Common name	Difenoconazole
Company experimental name	CGA-169374
IUPAC name	1-[2-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-4-methyl-[1,3]dioxolan-2-ylmethyl]-1*H*-[1,2,4]triazole
CAS name	1-[[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole
CAS registry number	119446-68-3
Chemical structure of CGA-205375 livestock metabolite	 mol. wt. 349.2
Chemical structure of 1,2,4-Triazole (1,2,4-T)	
Chemical structure of Triazolylalanine (TA)	

Table 3.1. Difenoconazole Nomenclature.	
Chemical structure of Triazolylacetic acid (TAA)	

3.2 Physical/Chemical Characteristics

The physicochemical properties of difenoconazole are reported in Appendix C.

3.3 Pesticide Use Pattern

Difenoconazole is proposed for new foliar uses on pea and bean, dried shelled, except soybean, subgroup 6C and bushberry subgroup 13-07B; new end-use product (EPA File Symbol 100-RLEO) for new post-harvest uses on pome fruit 11-10; and new end-use product (EPA File Symbol 100-RLNA) for new use to control fungal diseases on ornamental plants and vegetable transplants grown in both indoor and outdoor production facilities. All proposed uses are assumed to be of short-& intermediate-term duration, and all registered/proposed labels require occupational and other handlers to wear long-sleeved shirts, long pants, shoes, socks, and chemical resistant gloves.

For the new uses on pea and bean, dried shelled, except soybean, subgroup 6C and bushberry subgroup 13-07B, the registrant, Syngenta, is proposing to amend the following registered product: 2.08 lb ai/gal EC formulation of difenoconazole (Inspire™ Fungicide; EPA Reg. No. 100-1262) and the following multiple active ingredient (MAI) products: a 2.08 lb ai/gal MAI EC formulation with propiconazole (Inspire™ XT Fungicide; EPA Reg. No. 100-1312); a 1.05 lb ai/gal MAI suspension concentrate (SC) formulation with azoxystrobin (Quadris Top™ Fungicide; EPA Reg. No. 100-1313); and a 0.73 lb ai/gal MAI emulsion oil in water (EW) formulation with cyprodinil (Inspire Super ™ Fungicide; EPA Reg. No. 100-1317). The use directions are summarized in Table 3.3.1.

Table 3.3.1. Summary of Directions for Use of Difenoconazole for Proposed Uses on Legume Subgroup 6C and Bushberry Subgroup 13-07B.						
Appl. Timing, Type, and Equip.	**Formulation [EPA Reg. No.]**	**Max. Appl. Rate (lb ai/A)**	**Max. No. Appl. per Season**	**Max. Seasonal Appl. Rate (lb ai/A)**	**PHI (days)**	**Use Directions and Limitations**
Pea and bean, dried shelled (except soybean), subgroup 6C.						
Foliar, Broadcast, Ground (≥15 gal/A), aerial (≥10 gal/A) or chemigation (0.1-0.25 inches/A)	2.08 lb ai/gal EC [100-1262]	0.114-0.115	Not Specified (NS)	0.46	14	The minimum retreatment interval is 7 days. Make no more than 2 sequential applications before alternating to another fungicide with a different mode of action.
	1.05 lb ai/gal MAI SC [100-1313]					Same as for 100-1262.
Bean, dried (except cowpeas) Note: Because there are no currently established tolerances for residues of propiconazole and cyprodinil in/on dried peas, Syngenta is not proposing use of Inspire™ XT Fungicide (EPA Reg. No. 100-1312) and Inspire Super ™ Fungicide (EPA Reg. No. 100-1317) on dried peas.						
Foliar, Broadcast, Ground (≥15 gal/A), aerial (≥10 gal/A) or chemigation (0.1-0.25 inches/A)	2.08 lb ai/gal MAI EC [100-1312]	0.114-0.115	NS	0.46	14	The minimum retreatment interval is 7 days. Make no more than 2 sequential applications before alternating to another fungicide with a different mode of action.
	0.73 lb ai/gal MAI EW [100-1317]					Same as for 100-1312.
Bushberry subgroup 13-07B						
Foliar, Broadcast, Ground (≥15 gal/A) or aerial (≥10 gal/A)	2.08 lb ai/gal EC [100-1262]	0.114-0.115	NS	0.46	7	The minimum retreatment interval is 7 days. Make no more than 2 sequential applications before alternating to another fungicide with a different mode of action.
	2.08 lb ai/gal MAI EC [100-1312]				30	Same as for 100-1262.
	1.05 lb ai/gal MAI SC [100-1313]				7	Same as for 100-1262.
	0.73 lb ai/gal MAI EW [100-1317]				7	Same as for 100-1262.

PHI = preharvest interval.

For post-harvest dip, drench, flood, and spray uses on pome fruit group 11-10, Syngenta is proposing a new MAI end-use product, Academy™ Fungicide (EPA File Symbol 100-RLEO),

formulated as a flowable suspension concentrate (SC) containing both difenoconazole (20.9%; 2.06 lb ai/gal) and fludioxonil. Use directions are summarized in Table 3.3.2.

Table 3.3.2. Summary of Directions for Use of Difenoconazole for Post-harvest Uses on Pome Fruit Group 11-10.

Appl. Timing, Type, and Equip.	Formulation [EPA File Symbol]	Max. Appl. Rate (lb ai/unit)	Max. No. Appl. per Season	Max. Seasonal Appl. Rate	PHI	Use Directions and Limitations
Pome Fruit Group 11-10 Post-Harvest Use						
Bin/Truck Drench or In-Line Dip/Drench or Flooder	2.06 lb ai/gal SC [100-RLEO]	0.26 lb ai/100 gal.	1 Do not make more than 1 post-harvest application of Academy to fruit. Apply either once before storage or once after storage, just prior to marketing.	N/A	N/A	For in-line drench or dip applications, treat fruit for 15-30 seconds and allow fruit to drain. Fruit coatings may be applied separately after aqueous fungicide treatments.
In-Line Aqueous or Fruit Coating Spray Application		0.26 lb ai/200,000 lb of fruit				Mix the fungicide solution in an appropriate water, wax/oil emulsion, or aqueous dilution of a wax/oil emulsion for the crop being treated. Use T-jet, CDA, or similar application system.

PHI = Pre-Harvest Interval N/A = Not Applicable

Syngenta is requesting registration of a new MAI end-use product, Alibi Flora™ (EPA File Symbol 100-RLNA), formulated as a flowable suspension concentrate (SC) containing both difenoconazole (11.4%; 1.05 lb ai/gal) and azoxystrobin (18.2%; 1.67 lb ai/gal) which is identical in composition to already registered products Quadris Top™ (EPA Reg. No. 100-1313) and Briskway™ (EPA Reg. No. 100-1433). Alibi Flora™ (EPA File Symbol 100-RLNA) is proposed for new uses to control diseases in ornamentals and a variety of vegetable transplants produced for sale to residential consumers only, grown in greenhouses, shade houses, lath houses, other outdoor growing structures and outdoor nurseries. Alibi Flora™ (EPA File Symbol 100-RLNA) is proposed for use at a maximum single application rate (maximum total rate) of 0.13 lb ai/A/application (0.52 lb ai/A) to ornamental plants; 0.113-0.115 lb ai/A/application (0.45-0.46 lb ai/A) to *Brassica* Cole Leafy Vegetable transplants, dry bulb onion transplants, cucurbit vegetable transplants and fruiting vegetable (except tomato) transplants; 0.115 lb ai/A/application (0.34 lb ai/A) to green onion transplants; and 0.07 lb ai/A/application (0.39 lb ai/A) to tomato transplants. Use directions are summarized in Table 3.3.3.

Table 3.3.3. Summary of Directions for Use of Difenoconazole on Ornamental Plants and Vegetable Transplants.						
Site	**Applic. Equip.**	**Formulation [EPA File Symbol]**	**Applic. Rate (lb ai/A/applic.)**	**Max. Yearly/Crop[1] Applic. Rate (lb ai/A)**	**Last Applic. Prior to Shipping[2] (days)**	**Use Directions and Limitations**
Ornamental Plants						
Ornamental Plants (outdoors and greenhouse)	Aerial, Airblast Chemigation, Ground, Handheld	Liquid Alibi Flora™ [100-RLNA]	0.13 0.0011 lbai/gal	0.52	Not Specified	Apply every 7-21 days
Vegetable Transplants Commercially Produced for Sale to Residential Consumers Only						
Brassica Cole Leafy Vegetables	Aerial, Chemigation, Ground, Handheld	Liquid Alibi Flora™ [100-RLNA)	0.115	0.46	1	Apply every 7-14 days
Bulb Vegetables				0.34 – green onions 0.46 – dry bulb onions	7	Apply every 7-14 days
Cucurbit Vegetables				0.46	1	Apply every 7-14 days
Fruiting Vegetables			0.113	0.45	0	Apply every 7-10 days
Tomatoes			0.07	0.39	0	Apply every 7-10 days

1 For crops grown indoors – the maximum per crop rate is specified on the label, for crops grown outdoors, the maximum yearly application rate is specified on the label.

2 PHIs do not apply.

3.4 Anticipated Exposure Pathways

The Registration Division has requested an assessment of human health risk to support the proposed uses of difenoconazole on new foliar uses on pea and bean, dried shelled, except soybean, subgroup 6C and bushberry subgroup 13-07B; new end-use product (EPA File Symbol 100-RLEO) for new post-harvest uses on pome fruit 11-10; and new end-use product (EPA File Symbol 100-RLNA) for new use to control fungal diseases on ornamental plants and vegetable transplants grown in both indoor and outdoor production facilities. For domestic uses, humans may be exposed to difenoconazole in food and drinking water, since difenoconazole may be applied directly to growing crops and application may result in difenoconazole reaching surface and ground water sources of drinking water. There are also residential uses of difenoconazole, so there is exposure in residential or non-occupational settings. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is a potential for post-application exposure for workers re-entering treated fields.

Risk assessments have been previously conducted for the existing uses of difenoconazole. This risk assessment considers all of the aforementioned exposure pathways based on the proposed uses of difenoconazole, but also considers the existing uses as well.

3.5 Considerations of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf.

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 HAZARD CHARACTERIZATION AND DOSE-RESPONSE ASSESSMENT

4.1 Toxicology Studies Available for Analysis

The toxicology database for difenoconazole is complete for evaluating and characterizing difenoconazole toxicity and selecting endpoints for purposes of this risk assessment. All toxicity studies required in accordance with new 40 CFR Part 158 data requirements have been submitted. The Hazard and Science Policy Council (HASPOC) concluded that a 28-day inhalation toxicity study is not required at this time (TXR 0054074).

4.2 Absorption, Distribution, Metabolism and Excretion (ADME)

The absorption, distribution, metabolism, and excretion of difenoconazole were studied in rats. In one study, the test compound was labeled with C^{14} at either the phenyl or triazole ring. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg of radiolabeled compound or 0.5 mg/kg unlabeled compound by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C]-difenoconazole on day 15. In a second follow-up study [^{14}C]-difenoconazole (phenyl ring label) was administered as single oral gavage dose of 0.5 or 300 mg/kg. The second study was conducted to address deficiencies in the initial study by providing biliary excretion and identification of metabolites.

Difenoconazole was rapidly absorbed and extensively distributed, metabolized, and excreted in

rats for all dosing regimens. Distribution, metabolism and elimination of difenoconazole were not sex related in the first study. Recovery of administered dose was 96-108%. Biliary excretion, examined in the second study, constituted the main route of elimination with some dose and sex dependency (75% at the low dose for both sexes; 56% for males and 39% for females at the high dose). Urinary and fecal eliminations exhibited a dose-related pattern at 48 hours. In bile duct cannulated rats, 9-l4% of dose was eliminated in the urine at the low dose versus 1% in the high-dose rats. In bile duct cannulated rats, 2-4% was eliminated in the feces at the low dose versus 17-22% at the high dose. Half-lives of elimination are approximately 20 hours for the low dose groups and 33-48 hours for the high dose group. Radioactivity in the blood peaked at 2 to 4 hours at the low and high dose respectively.

Difenoconazole undergoes successive oxidation and conjugation reactions. Following administration of 300 mg/kg of (^{14}C-phenyl) difenoconazole, three major urinary metabolites were identified as CGA 205375 and HO-CGA 205375 (6% of dose), sulfate conjugates (and their isomers) of HO-205375 (3.9% of dose), and the hydroxyacetic metabolite of HO-CGA 205375 (2.0% of dose). No single unknown urinary metabolite accounted for >1.1% of the dose. Free triazole metabolite was detected in the urine of the triazole-label groups and its byproduct was detected in the liver of phenyl labeled groups only.

The study results indicate that difenoconazole and/or its metabolites do not bioaccumulate appreciably following oral exposure since all tissues contained negligible levels (<1%) or radioactivity 7 days post exposure.

A dermal absorption factor of 6% was derived based on data from a triple pack of a rat *in vivo* dermal absorption study and *in vitro* dermal absorption studies conducted with rat and human skin (TXR 0056473). Inhalation toxicity is assumed to be equivalent to oral toxicity.

4.3 Toxicological Effects

Subchronic and chronic studies with difenoconazole in mice and rats showed decreased body weights, decreased body weight gains and effects on the liver (e.g. hepatocellular hypertrophy, liver necrosis, fatty changes in the liver). No systemic toxicity was observed at the limit dose in the most recently submitted 28-day rat dermal toxicity study.

The available toxicity studies indicated no increased susceptibility of rats or rabbits from *in utero* or postnatal exposure to difenoconazole. In prenatal developmental toxicity studies in rats and rabbits and in the two-generation reproduction study in rats, fetal/offspring toxicity, when observed, occurred at equivalent or higher doses than in the maternal/parental animals.

In a rat developmental toxicity study, developmental effects were observed at doses higher than those which caused maternal toxicity. Developmental effects in the rat included increased incidence of ossification of the thoracic vertebrae and hyoid, decreased number of sternal centers of ossification, increased number of ribs and thoracic vertebrae, and decreased number of lumbar vertebrae. In the rabbit study, developmental effects (increases in post-implantation loss and resorptions and decreases in fetal body weight) were also seen at maternally toxic (decreased body weight gain and food consumption) doses. In the two-generation reproduction study in

rats, toxicity to the fetuses/offspring, when observed, occurred at equivalent or higher doses than in the maternal/parental animals.

In an acute neurotoxicity study in rats, reduced fore-limb grip strength was observed on day 1 in males at the LOAEL of 200 mg/kg. The effect in males is considered transient since it was not observed at later observation points. Toxicity in females was observed only at the limit dose (2000 mg/kg). In a subchronic neurotoxicity study in rats, decreased hind limb strength was observed in males only at ≥ 17.5 mg/kg/day doses. The effects observed in acute and subchronic neurotoxicity studies are transient, and the dose-response is well characterized with identified NOAELs. Based on the toxicity profile, and lack of concern for neurotoxicity, a developmental neurotoxicity study in rats is not required.

In an immunotoxicity study in mice difenoconazole produced immunotoxicity at doses that caused systemic toxicity.

In accordance with HED's current policy and EPA's 2005 Cancer Guidelines, difenoconazole is classified as "Suggestive Evidence of Carcinogenic Potential" based on liver tumors observed in mice at 300 ppm and higher, the absence of tumors at two lower doses of 10 and 30 ppm, excessive toxicity observed at the two highest doses of 2500 and 4500 ppm, the absence of genotoxicity and no evidence of carcinogenicity in rats (TXR 0054532). HED's Cancer Peer Review Committee recommended use of an MOE approach to risk assessment using the chronic point of departure (POD) based on effects observed in the chronic mouse study relevant to tumor development (*i.e.*, hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis). The POD is considered protective of the cancer effects.

Difenoconazole possesses low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not an eye or skin irritant and is not a sensitizer.

The complete toxicity profile for difenoconazole is provided in Appendix A.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

The FQPA factor for increased susceptibility to infants and children is reduced to 1x

4.4.1 Completeness of the Toxicology Database

The toxicity database is sufficient for a full hazard evaluation and is considered adequate to evaluate risks to infants and children. The Hazard and Science Policy Council (HASPOC) concluded that a 28-day inhalation toxicity study is not required at this time (TXR 0054074).

4.4.2 Evidence of Neurotoxicity

There are no clear signs of neurotoxicity following acute, subchronic or chronic dosing in multiple species in the difenoconazole database. The effects observed in acute and subchronic neurotoxicity studies are transient, and the dose-response is well characterized with identified NOAELs.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

The available Agency guideline studies indicated no increased qualitative or quantitative susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to difenoconazole. In the prenatal developmental toxicity studies in rats and rabbits and the two-generation reproduction study in rats, toxicity to the fetuses/offspring, when observed, occurred at equivalent or higher doses than in the maternal/parental animals.

In a rat developmental toxicity study developmental effects were observed at doses higher than those which caused maternal toxicity. In the rabbit study, developmental effects (increases in post-implantation loss and resorptions and decreases in fetal body weight) were also seen at maternally toxic doses (decreased body weight gain and food consumption). In the two-generation reproduction study in rats, toxicity to the fetuses/offspring, when observed, occurred at equivalent or higher doses than in the maternal/parental animals.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The dietary risk assessment is conservative (tolerance level residues and 100% crop treated for the acute while the chronic used USDA Pesticide Data Program (PDP) monitoring data, average field trial residues for some commodities, tolerance level residues for remaining commodities, and average percent crop treated for some commodities) and will not underestimate dietary exposure to difenoconazole.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

Toxicity endpoints and points of departure (PODs) for dietary (food and water), occupational, and residential exposure scenarios are summarized below. A detailed description of the studies used as a basis for the selected endpoints are presented in Appendix A.

An acute POD of 25 mg/kg/day (NOAEL) was selected from an acute neurotoxicity study in rats based on reduced fore-limb grip strength in males on day 1 at the LOAEL of 200 mg/kg/day. An uncertainty factor (UF) of 100x (10x to account for interspecies extrapolation and 10x for intraspecies variation) was applied to the NOAEL to obtain an acute reference dose (aRfD) of 0.25 mg/kg/day. Since the FQPA factor has been reduced to 1X, the acute population adjusted dose (aPAD) is equivalent to the aRfD. The selected endpoint is considered appropriate for acute dietary exposure because effects were seen after a single dose. The endpoint is protective of the general population and all subpopulations for effects seen in the acute neurotoxicity study in rats. It is also protective of developmental and maternal effects observed in the rabbit developmental toxicity study at the LOAEL of 75 mg/kg/day and NOAEL of 25 mg/kg/day.

A chronic POD of 0.96 mg/kg/day (NOAEL) was selected from a chronic toxicity/carcinogenicity oral study in rats based on cumulative decreases in body weight gains in males observed at the LOAEL of 24 mg/kg/day. A UF of 100x (10x to account for interspecies extrapolation and 10x for intraspecies variation) was applied to the dose to obtain a chronic

reference dose (cRfD/cPAD) of 0.01 mg/kg/day. Since the FQPA factor has been reduced to 1X, the chronic population adjusted dose (cPAD) is equivalent to the cRfD.

Short-term incidental oral and short- and intermediate term dermal and inhalation PODs of 1.25 mg/kg/day were selected from a two generation reproduction study in rats based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21, and reductions in body weight gain in F0 females. Although dermal toxicity studies are available, a POD from an oral study was selected because effects in young animals (decreased pup weight) the primary effect of concern for short, intermediate and long term exposure is not specifically evaluated in the available dermal toxicity studies that only assess adult animals. The selected endpoint is protective of offspring effects from dermal exposure. An MOE of 100 is the level of concern (LOC) for the short- and intermediate-term dermal and inhalation exposure scenarios based on the conventional uncertainty factor of 100 (10x for interspecies extrapolation and 10x for intraspecies variation). There are no residential uses for difenoconazole that would result in incidental oral exposure to children.

A dermal absorption factor (DAF) is applied when dermal exposure endpoints are selected from oral toxicity studies. The dermal factor converts the oral dose to an equivalent dermal dose for the risk assessment. A DAF of 6% was selected for use in risk assessment based on available *in vivo* dermal absorption studies in rat and *in vitro* dermal absorption studies conducted with rat and human skin (TXR 0056473).

4.5.2 Recommendations for Combining Exposure Routes for Risk Assessment

When there are potential residential exposures to the pesticide, the aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. There are potential residential post-application exposures to adults via the dermal route and to children via dermal and incidental oral routes of exposure. Oral, dermal and inhalation exposures to residents should be aggregated for difenoconazole because the endpoints selected for these exposure routes are based on common toxicological effects (body weights).

4.5.3 Cancer Classification and Risk Assessment Recommendations

Difenoconazole is not mutagenic, and no evidence of carcinogenicity was seen in rats. Evidence for carcinogenicity was seen in mice, where liver tumors were induced at doses which were considered to be excessively high for carcinogenicity testing. Liver tumors were observed in mice at 300 ppm and higher; however, based on excessive toxicity observed at the two highest doses of 2500 and 4500 ppm (females terminated after two weeks due to excessive toxicity resulting in moribundity and death), the absence of tumors at two lower doses of 10 and 30 ppm, the absence of genotoxic effects, and no evidence of carcinogenicity in rats. In accordance with HED's current policy and EPA's 2005 Cancer Guidelines, difenoconazole is classified as "Suggestive Evidence of Carcinogenic Potential," based on excessive toxicity observed at the two highest doses, the absence of tumors at the lower doses and the absence of genotoxic effects (TXR 0054532). Based on the CPRC recommendation, the risk assessment uses an (MOE) approach utilizing the no-observable-adverse-effects-level (NOAEL) of 30 ppm (4.7 and 5.6 mg/kg/day in males and females, respectively) and the lowest-observable-adverse-effects-level

(LOAEL) of 300 ppm (46 and 58 mg/kg/day in males and females, respectively) from the mouse study using only those biological endpoints which were relevant to tumor development (*i.e.*, hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis). The chronic POD of 0.96 mg/kg/day selected based on bodyweight effects is protective of the cancer effects.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Risk Assessment

Toxicological doses/endpoints selected for the difenoconazole risk assessment are provided in Tables 4.5.4.1 and 4.5.4.2.

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Relevant Toxicological Effects
Acute Dietary (All populations)	NOAEL = 25 mg/kg	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	aRfD = aPAD = 0.25 mg/kg/day	Acute Neurotoxicity Study in Rats (MRID 46950327) LOAEL= 200 mg/kg in males based on reduced fore-limb grip strength in males on day 1.
Chronic Dietary (All populations)	NOAEL = 0.96 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	cRfD = cPAD = 0.01mg/kg/day	Combined chronic toxicity/carcinogenicity (rat; dietary, MRID 42090019, 42710010) LOAEL = 24.1/32.8 mg/kg/day (M/F) based on cumulative decreases in body-weight gains.
Incidental Oral Short-Term (1-30 days)	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary, MRID 42090018) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months) DAF = 6%	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary, MRID 42090018) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Inhalation (Short- and Intermediate-term) Inhalation and oral absorption assumed equivalent	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary, MRID 42090018) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Cancer (oral, dermal, inhalation)	Difenoconazole is classified "Suggestive Evidence of Carcinogenic Potential" with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P. V. Shah			

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, LOC for Risk Assessment**	**Study and Relevant Toxicological Effects**
	dated March 3, 2007, HED Doc. No. 0054532).			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies DAF = Dermal Absorption Factor

Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for Difenoconazole for Use Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months) DAF = 6%	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE<100	Reproduction and fertility Study (rat; dietary, MRID 42090018) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Inhalation (Short- and Intermediate-term) Inhalation and oral absorption assumed equivalent	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE<100	Reproduction and fertility Study (rat; dietary, MRID 42090018) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Cancer (oral, dermal, inhalation)	Difenoconazole is classified "Suggestive Evidence of Carcinogenic Potential" with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P. V. Shah dated March 3, 2007, HED Doc. No. 0054532).			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

5.0 DIETARY EXPOSURE AND RISK ASSESSMENT

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

The nature of the residue in plants is understood based on acceptable plant metabolism studies reflecting foliar applications in canola, grape, potato, tomato, and wheat, and seed treatment in wheat. The residue of concern for both tolerance enforcement and risk assessment for crops included in this petition is difenoconazole only. The nature of the residue in livestock is understood based on acceptable goat and hen metabolism studies. The residues of concern for

both tolerance enforcement and risk assessment for livestock commodities are difenoconazole and its metabolite CGA-205375. In addition, metabolite OH-CGA-169374, which comprised 15% of the TRR in goat milk from the phenyl-labeled study, should be considered as a residue of concern in milk for the dietary risk assessment.

The nature of the residue in rotational crops is adequately understood. The metabolism of difenoconazole in rotational crops is similar to that of primary crops. The available difenoconazole confined and limited field rotational crop trials are deemed adequate to satisfy data requirements under Guidelines 860.1850 and 860.1900. Taken together, these data support a 30-day plantback interval (PBI) for cereal and root/tuber crops not already registered for foliar use with difenoconazole and a 60-day PBI for all other crops not already registered for foliar use with difenoconazole. With these PBIs, tolerances for residues of difenoconazole are not needed for rotational crops.

Structures and names of difenoconazole metabolites are provided in Appendix B.

5.1.2 Summary of Environmental Degradation

Difenoconazole has potential to reach surface water via run-off, erosion, and spray drift, and is less likely to reach ground water except in soils of high sand and low organic matter content. Environmental fate data indicate that difenoconazole is relatively stable to aerobic and anaerobic soil metabolisms and aerobic and anaerobic aquatic metabolism. When applied at 0.1-0.23 ppm to an aerobic soil, difenoconazole appears to degrade with half-lives ranging from 84.5 to 533 days based on laboratory studies conducted on a variety of foreign and domestic soils. At concentrations of 10 ppm, difenoconazole degraded with the half-lives of 1059-1600 days in aerobic, and 947 days anaerobic loam soil, respectively. In aquatic environment under aerobic conditions, difenoconazole microbially degraded with half-lives ranging from 315 to 565 days at concentrations up to 0.17 mg ai/L, and 860 days in a concentration of 10 mg ai/L. Under anaerobic conditions, difenoconazole degraded in 370 days at a concentration of 0.04 mg ai/L, and 1245 days at concentrations of 10 mg ai/L. The longer half-life values obtained for those higher concentration rates may imply that the rate of difenoconazole microbially mediated degradation may be concentration dependent. In laboratory studies on difenoconazole a significant amount of radioactivity was nonextractable (14.4 to 48.9%) from soils.

Considering abiotic degradation, difenoconazole is photolyzed in water (half-life of 6 to 228 days), but stable in soil. The half-life of 228 days was extrapolated from a 15-day study in which difenoconazole slowly photolyzed from 100% to 91% under artificial light conditions (MRID 46950105). Also, the compound is stable to hydrolysis at pH values from 4 to 9.

Difenoconazole degraded with half-lives ranging from 139 to 462 days in the terrestrial field dissipation studies. The overall stability of the compound in the terrestrial environment suggests that difenoconazole may accumulate in soil with successive applications from year to year.

5.1.3 Comparison of Metabolic Pathways

Little information is available on the toxicity of the major difenoconazole metabolites. The

CGA-205375 metabolite formed in livestock appears to be formed in the rat also and is, therefore, part of the total toxic exposure for these animals.

5.1.4 Residues of Concern Summary and Rationale

Residues of concern were determined based on recommendations from the HED Residues of Concern Knowledgebase Sub-committee (ROCKS) (D391350, 9/19/11). The residue of concern for plant commodities for tolerance enforcement and risk assessment purposes is difenoconazole only. The HED ROCKS has determined that the parent compound and the CGA-205375 metabolite are the residues of concern in livestock commodities for both the tolerance enforcement and the risk assessment. In addition, metabolite OH-CGA-169374, which comprised 15% of the TRR in goat milk from the phenyl-labeled study, should be considered as a residue of concern in milk for the dietary risk assessment. Based on available goat metabolism data, total residues of concern in milk for dietary risk assessments (parent, CGA-205375 and OH-CGA-169374), should be calculated by multiplying the tolerance in milk by a factor of 1.5x. Table 5.1.4 summarizes tolerance expression and the residues of concern in plant and livestock commodities.

Difenoconazole belongs to the triazole group of fungicides. The triazole metabolites common to the group, 1,2,4-triazole (1,2,4-T), triazolylalanine (TA) and triazolylacetic acid (TAA), are residues of concern for risk assessment purposes and are assessed separately from the parent compound.

Table 5.1.4. Difenoconazole Residues of Concern in Plants and Ruminants.

Matrix		Residues of Concern	
		For Risk Assessment	For Tolerance Expression
Plants	Primary and Rotational crops	Parent Only	Parent Only
Livestock	Ruminant and Poultry	Parent and CGA 205375	Parent and CGA 205375
	Milk	Parent, CGA 205375 and OH-CGA-169374	Parent and CGA 205375
Drinking Water		Parent and CGA 205375	NA

Note: The triazole-containing metabolites 1,2,4-T, TA, and TAA should be included in the residues of concern for risk assessment purposes only for plant and livestock commodities. Since these metabolites are common to the entire class of traizole-derivative fungicides and because of differential toxicity between metabolites and the various parent compounds, risks associated with exposure to 1,2,4-T and to TA/TAA are addressed separately.

5.2 Food Residue Profile

5.2.1 Residues in Crops

Pending further amendments to the proposed uses on pea and bean, except soybean, subgroup 6C (See requirements under Section 2.3 Label Recommendations), the submitted/available residue chemistry data are adequate for tolerance determination for the proposed uses and risk assessment. Residues of difenoconazole in/on dried pea/bean seed ranged from less than the limit of quantitation (LOQ; <0.01 ppm) to 0.134 ppm. Residues of difenoconazole in/on blueberry, apple and pear were all detectable with maximum residues of 2.2 ppm, 2.61 ppm and 1.62 ppm, respectively. No residue decline data were submitted with the apple/pear data;

however, residue decline data for dried pea seed, dried bean seed and blueberry indicate that residues of difenoconazole may decrease with pre-harvest intervals (PHIs) greater than those proposed. Residues of difenoconazole do not concentrate in apple juice. The minimum proposed plant-back intervals are adequate to ensure that detectable residues of difenoconazole are not incurred in rotational crops.

Using the Organization for Economic Cooperation and Development (OECD) tolerance calculation procedures and in in accordance with the requirements for establishing tolerances for crop groups, the recommended tolerances are 0.20 ppm in/on pea and bean, except soybean, subgroup 6C, 40 ppm in/on pea hay, 10 ppm in/on pea vines, 4.0 ppm in/on bushberry subgroup 13-07B and 5.0 ppm in/on fruit, pome, group 11-10. The new pea hay and vine feedstuffs significantly increased the dietary burden calculation for dairy cattle. Based on the re-calculated livestock dietary burdens and available feeding study data, the currently established tolerance for residues of difenoconazole and its metabolite CGA-205375, expressed as difenoconazole equivalents, in milk should be increased from 0.01 ppm to 0.02 ppm to support the proposed new uses on dried peas. Other currently established livestock commodity tolerances remain adequate.

No new residue chemistry data were submitted in support of the proposed uses of difenoconazole formulated as a flowable suspension concentrate (SC; Alibi Flora™; EPA File Symbol 100-RLNA) to control diseases in *Brassica* Cole leafy vegetable, onion, cucurbit and fruiting vegetable transplants, grown in greenhouses for sale to residential consumers only. However, difenoconazole formulated as a SC (i.e., Quadris Top™; EPA Reg. No. 100-1313) is already registered for use on these same vegetables at the proposed maximum use rates but for late-season foliar applications and short PHIs (0- to 7-days). Hence, existing tolerances will cover the requested new vegetable transplant uses.

Residues of the triazole metabolites were determined in/on dried pea seed, dried bean seed and blueberry and detectable residues of TA were found in these commodities with maximum residues of 0.840 ppm, 2.48 ppm and 0.041 ppm, respectively. Residues of 1,2,4-T and TAA were less than the LOQ with the exception of residues of TAA in/on some of the dried bean seed samples (maximum residue 0.0373 ppm). Residues of the triazole metabolites may increase with increasing PHIs. [Note: Residues of the triazole metabolites were not determined in/on apple/pear; however, for the proposed post-harvest uses on pome fruit, anticipated residues of the triazole metabolites may be based on the incurred residues of parent adjusted for molecular weight for the proposed post-harvest uses.]

5.3 Water Residue Profile

5.3.1 Estimated Drinking Water Concentrations

This assessment provides estimated drinking water concentrations (EDWCs) of difenoconazole and its major metabolite, CGA-205375 (M1) in surface water and groundwater in support of human health risk assessment on the Interregional Research Project Number 4 (IR4) proposed new uses on ginseng, artichoke, and conversion on stone fruit group 12-12 and tree nut group 14-12. The Residues of Concern Knowledgebase Subcommittee (ROCKS) of the Health Effects Division (HED) recommended to include CGA-205375 as a residue of concern for drinking

water (USEPA, 2011, DP 391350). Therefore, this drinking water assessment was performed using total toxic residue (TTR; i.e. parent plus CGA 205375) method in support of the proposed Section 3 new uses following the approach used in a previous drinking water assessment for canola (US EPA 2013a, DP412614). Foliar spray applications (both aerial and ground spray applications) and chemigation, are being proposed for these crops. The EDWCs of difenoconazole and its major metabolite, CGA-205375 (M1) were generated using application rates of 0.46 to 0.52 lbs a.i./A.with the Surface Water Concentration Calculator model for surface water as well as the maximum application rate of 0.52 lbs a.i./A with the PRZM-GW and SCI-GROW models for groundwater.

The Interregional Research Project Number 4 (IR-4) also revised the existing crop groupings by converting stone fruit Group 12 to stone fruit Group 12-12 and nut tree Group 12 to nut tree Group 14-12. Since there are no changes in the application rates and methods for the revised crop groupings, previous drinking water assessments (stone fruit; USEPA, 2010; DP426124 and tree nut; USEPA 2009, DP340378) fulfill the requirement for refining EDWCs for these crops. EFED noticed that the application rate for cucurbit is higher in the submitted Inspire Super (EPA Reg. No. 100-1317) label as compared to previous label, which was stamped on August 03, 2012. Since the maximum applicant rate of 0.52 lbs a.i./A for cucurbit is higher than previously assessed application rate of 0.46 lbs a.i./A (USEPA 2009; DP361398 the EDWCs for the revised rate of cucurbit was reassessed.

Surface water and groundwater modeling were conducted for the maximum annual application rate of 0.46 to 0.52 lbs a.i./A for aerial application only as aerial applications produce conservative estimates. Remaining model input parameters were chosen according to current guidance (USEPA, 2009 and USEPA, 2013b). For surface water, the EDWCs for new uses and the revised application rate for cucurbit did not exceed the previously recommended peak (acute) concentration of 20.0 µg/L, annual mean (non-cancer chronic) concentration of 13.6 µg/L and the 30 year annual average concentration (cancer chronic) of 9.9 µg/L reported in the drinking water assessment based on grape use (US EPA, 2013; DP 398836). Recently, PRGM-GW scenarios were revised and consequently the estimated PZRM-GW groundwater concentrations were reduced to 1.77 µg/L from 2.24 µg/L and chronic concentration of 0.66 µg/L from 0.78 µg/L for the maximum application rate for FL citrus scenario. Recommended surface water and groundwater EDWCs for human health are listed in (Table 5.3.1.2).

Table 5.3.1.2. Tier II Drinking Water Exposure Estimates for Total Toxic Residues of Difenoconazole

Source	Peak Exposure (µg/L)	Annual Mean Exposure (µg/L)	30-year Average Exposure (µg/L)
Surface water	20.0	13.6	9.9
Groundwater[1]	2.24	---	0.82

[1] Groundwater EDWCs are based on PRZM-GW 100 years simulation and the highest application rate for difenoconazole

Drinking Water Data for Free Triazoles

Residues of 1,2,4-triazole in drinking water were provided to HED by the EFED (I. Maher, DP320682, 28 Feb 2006). Due to the inter-conversion between 1,2,4-triazole, triazole alanine, and triazole acetic acid that may occur in the environment, the residue estimates used in these

assessments are a summation of all three residues and, therefore, represent an overestimate of actual concentrations of the common triazole metabolites in drinking water. The Tier II PRZM/EXAMS (surface water) and SCIGROW (ground water) residue estimates are summarized in Table 5.3.1.3. HED notes that there were no detects of 1,2,4-triazole in any of the 271 water samples analyzed by PDP, with a limit of quantification of 730 parts-per-trillion (0.73 ppb). The surface water estimates are significantly greater than those for ground water, and were used in the assessments for free triazole as well as the conjugated metabolites. EFED stated that the new metconazole uses are covered by the previous drinking water assessment for 1,2,4-triazole (DP320682, I. Maher, 2/28/06).

Table 5.3.1.3. Summary of Estimated Drinking Water Concentrations of 1,2,4-Triazole.

Exposure Duration	Surface Water Concentration, ppm	Ground Water Concentration, ppm
Acute	0.041	0.001
Chronic	0.011	0.001

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

Screening level acute and refined chronic dietary and drinking water exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database DEEM-FCID, Version 3.16. This software uses 2003-2008 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA). Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic dietary assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to the reference dose (RfD) divided by the additional Safety Factor, if applied. For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The acute dietary exposure analyses assumed 100% crop treated (CT). Average %CT was used in the chronic dietary exposure analysis for the following crops: almond 5%, cabbage 2.5%, cucumbers 5%, garlic 5%, grape 5%, grapefruit 2.5%, onions 5%, orange 2.5%, pecan 2.5%, peach 1%, peppers 2.5%, pistachio 2.5%, pumpkin 2.5%, squash 5%, strawberry 2.5%, sugar beets 15%, tangerine 2.5%, tomatoes 25%, walnut 2.5%, watermelon 5%, and wheat 10%.

5.4.3 Acute Dietary Risk Assessment

A new dietary assessment was conducted for the proposed new uses. The proposed uses results dietary risk estimates below HED's level of concern; see Table 5.4.1.1. The highest is all infants <1 years resulting in 49% of the aPAD.

Table 5.4.3.1. Summary of Acute Dietary (Food plus Water) Exposure and Risk for Difenoconazole at the 95th Percentile.			
Population Subgroup	**aPAD (mg/kg/day)**	**Exposure (mg/kg/day)**	**%aPAD**
General U.S. Population	0.25	0.038393	15
All Infants (< 1 year old)		**0.122946**	**49**
Children 1-2 years old		0.108065	43
Children 3-5 years old		0.074001	30
Children 6-12 years old		0.050176	20
Youth 13-19 years old		0.024832	9.9
Adults 20-49 years old		0.025978	10
Adults 50-99 years old		0.028841	12
Females 13-49 years old		0.025939	10

The bolded %aPAD is the highest.

Dietary Assessment of Free Triazole and its Conjugates

Reference: Common Triazole Metabolites: Updated Dietary (Food + Water) Exposure and Risk Assessment to Address The New Section 3 Registrations For Use of Propiconazole on Rapeseed Crop Subgroup 20A; Use of Difenoconazole on Rapeseed Crop Subgroup 20A; and Use of Tebuconazole on Imported Oranges.. *T. Morton, DP414951.drs, 10/24/13.*

The dietary exposure analyses for the triazole metabolites (D414951, T. Morton, 24 Oct. 2013) was previously updated. Addition of these uses did not significantly change the dietary exposure for the triazole metabolites. The results from the triazole dietary analysis are below HED's level of concern; see Table 5.4.1.2.

Table 5.4.3.2. Summary of Dietary (Food and Drinking Water) Exposure and Risk for the Common Triazole Metabolites.						
Population Subgroup	**Acute Dietary (95th Percentile)**		**Chronic Dietary**		**Cancer**	
	Dietary Exposure (mg/kg/day)	**% aPAD***	**Dietary Exposure (mg/kg/day)**	**% cPAD***	**Dietary Exposure (mg/kg/day)**	**Risk**
1,2,4-Triazole						
General U.S. Population	0.008240	27	0.001276	26	Not Applicable	Not Applicable
All Infants (< 1 year old)	0.012026	40	0.001822	36		
Children 1-2 years old	**0.022883**	**76**	**0.003629**	**73**		
Children 3-5 years old	0.018815	63	0.002896	58		
Children 6-12 years old	0.010932	36	0.001588	32		
Youth 13-19 years old	0.007167	24	0.001036	21		
Adults 20-49 years old	0.006581	22	0.001101	22		
Adults 50+ years old	0.005808	19	0.001036	21		
Females 13-49 years old	0.006730	22	0.001073	22		
Triazolylalanine + Triazolylacetic Acid+Triazolylpyruvic acid						
General U.S. Population	Not Applicable	Not Applicable	0.017658	20	Not Applicable	Not Applicable
All Infants (< 1 year old)			0.021510	24		
Children 1-2 years old			**0.054965**	**61**		
Children 3-5 years old			0.044098	49		
Children 6-12 years old			0.023459	26		
Youth 13-19 years old			0.014759	16		
Adults 20-49 years old			0.014662	16		

Table 5.4.3.2. Summary of Dietary (Food and Drinking Water) Exposure and Risk for the Common Triazole Metabolites.						
Population Subgroup	**Acute Dietary (95th Percentile)**		**Chronic Dietary**		**Cancer**	
	Dietary Exposure (mg/kg/day)	**% aPAD***	**Dietary Exposure (mg/kg/day)**	**% cPAD***	**Dietary Exposure (mg/kg/day)**	**Risk**
Adults 50+ years old			0.013721	15		
Females 13-49 years old	**0.078443**	**78**	0.014260	16		

* The values for the highest exposed population for each type of risk assessment are bolded.

5.4.4 Chronic Dietary and Drinking Water Analysis

A new dietary assessment was conducted for the proposed uses of difenoconazole and results in dietary risk estimates below HED's level of concern; see Table 5.4.2.

Table 5.4.4. Summary of Chronic Dietary (Food plus Water) Exposure and Risk for Difenoconazole.			
Population Subgroup	**cPAD (mg/kg/day)**	**Exposure (mg/kg/day)**	**%cPAD**
General U.S. Population	0.01	0.002554	26
All Infants (< 1 year old)		0.007683	77
Children 1-2 years old		**0.008828**	**88**
Children 3-5 years old		0.006009	60
Children 6-12 years old		0.003676	37
Youth 13-19 years old		0.001980	20
Adults 20-49 years old		0.001847	19
Adults 50-99 years old		0.002068	21
Females 13-49 years old		0.001814	18

The bolded %cPAD is the highest.

5.4.5 Summary Table

Table 5.4.5. Summary of Dietary Exposure and Risk for Difenoconazole FOOD PLUS DRINKING WATER.						
Population Subgroup	**Acute Dietary (95th Percentile)**		**Chronic Dietary**		**Cancer**	
	Dietary Exposure (mg/kg/day)	**% aPAD**	**Dietary Exposure (mg/kg/day)**	**% cPAD**	**Dietary Exposure (mg/kg/day)**	**Risk**
General U.S. Population	0.038393	15	0.002554	26	N/A	
All Infants (< 1 year old)	**0.122946**	**49**	0.007683	77		
Children 1-2 years old	0.108065	43	**0.008828**	**88**		
Children 3-5 years old	0.074001	30	0.006009	60		
Children 6-12 years old	0.050176	20	0.003676	37		
Youth 13-19 years old	0.024832	9.9	0.001980	20		
Adults 20-49 years old	0.025978	10	0.001847	19		
Adults 50-99 years old	0.028841	12	0.002068	21		

Table 5.4.5. Summary of Dietary Exposure and Risk for Difenoconazole FOOD PLUS DRINKING WATER.						
Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk
Females 13-49 years old	0.025939	10	0.001814	18		

6.0 RESIDENTIAL (NON-OCCUPATIONAL)EXPOSURE/RISK CHARACTERIZATION

Based on the proposed and existing exposure pattern, residential exposure scenarios have been identified from treatment of ornamental plants in commercial and residential landscapes and interior plantscapes. Potential exposure is expected to homeowners handling the product and/or from performing post-application activities in treated areas.

Representative outdoor and indoor residential handler and post-application exposure scenarios were previously reassessed for all difenoconazole uses using the Revised Residential SOPs (2012), and the risk estimates were not of concern. (D412811; I. Nieves; 11/13/13). This evaluation covers both the proposed and previously assessed residential uses for difenoconazole, and is summarized in this document for the purposes of the aggregate risk assessment. Table 6.0.1 presents a summary of the residential handler non-cancer exposure and risk estimates for the proposed and already registered scenarios (MOEs ranged from 3,500 to 68,000; LOC =100). Table 6.0.2 summarizes the residential post-application non-cancer exposure and risk estimates for all difenoconazole uses (MOEs ranged from 250 to 31,000; LOC=100). The proposed uses of difenoconazole will not impact the human health aggregate risk assessment.

Table 6.0.1. Residential Handler Non-cancer Exposure and Risk Estimates for Difenoconazole.										
Exposure Scenario	Level of Concern	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (mg/lb ai)	Maximum Application Rate[1]	Area Treated or Amount Handled Daily[2]	Dermal		Inhalation		Total
						Dose (mg/kg/day)[3]	MOE[4]	Dose (mg/kg/day)[5]	MOE[6]	MOE[7]
Mixer/Loader/Applicator on Ornamentals (Garden/Trees) with Liquid Formulation										
Manually-pressurized handwand	100	63	0.018	3.0×10^{-6} lb ai/ft^2 (0.13 lb ai/A)	1,200 ft^2	0.00017	7,400	0.0000008	1,600,000	7,400
Hose-end Sprayer		58	0.0014			0.00016	8,000	0.000000063	20,000,000	8,000
Backpack		130	0.14			0.00035	3,600	0.0000063	200,000	3,500
Ready-to-use Hose-end Sprayer		6.26	0.034			0.000017	74,000	0.0000015	820,000	68,000

1 Based on registered label (EPA Reg. No. 100-1262)
2 Based on HED's 2012 Residential SOPs (http://www.epa.gov/pesticides/science/residential-exposure-sop.html).
3 Dermal Dose = Dermal Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) × Dermal Absorption Factor (%) ÷ Body Weight (kg).
4 Dermal MOE = Dermal NOAEL (mg/kg/day) ÷ Dermal Dose (mg/kg/day).
5 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) ÷ Body Weight (kg).
6 Inhalation MOE = Inhalation NOAEL (mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

7 Total MOE = NOAEL (mg/kg/day) ÷ (Dermal Dose + Inhalation Dose).

Table 6.0.2 Residential Post-application Non-cancer Exposure and Risk Estimates for Difenoconazole.					
Lifestage	**Post-application Exposure Scenario**		**Application Rate[1]**	**Dose (mg/kg/day)[2]**	**MOEs[3]**
	Use Site	**Route of Exposure**			
Adult	Gardens	Dermal	0.13 lb ai/A	0.005	250
Child 6 < 11 yrs				0.003	360
Adult	Trees and Retail Plants			0.00046	2,700
Child 6 < 11 yrs				0.00031	4,000
Adult	Indoor Plants			0.000060	21,000
Child 6 < 11 yrs				0.000041	31,000
Adult	Golfing	Dermal	0.25 lb ai/A	0.00044	2,800
Child 11 <16 years				0.00051	2,400
Child 6 < 11 yrs				0.00060	2,100

1. Based on registered or proposed label (Reg. No. 100-1262).
2. Dose (mg/kg/day) equations provided in Appendix [**A**].
3. MOE = POD (mg/kg/day) ÷ Dose (mg/kg/day).

Table 6.0.3 reflects the residential risk estimates that are recommended for use in the aggregate assessment for difenoconazole.

- The recommended residential exposure for use in the adult aggregate assessment reflects dermal and inhalation exposure from mixing/loading/applying difenoconazole with a backpack sprayer.
- The recommended residential exposure for use in the adult aggregate assessment reflects dermal exposure from post-application exposure to garden applications.
- The recommended residential exposure for use in the children 6 to 11 years old aggregate assessment reflects dermal exposure from post-application exposure to garden applications.

Table 6.0.3. Recommendations for the Residential Exposures for the Difenoconazole Aggregate Assessment.[1]								
Lifestage (Scenario)	**Dose (mg/kg/day)[2,4]**				**MOE[3,5]**			
	Dermal	**Inhalation**	**Oral**	**Total**	**Dermal**	**Inhalation**	**Oral**	**Total**
Residential Handler								
Adult (Backpack Sprayer)	0.00035	0.0000063	N/A	0.00036	3,600	200,000	N/A	3,500
Residential Post-application								
Adult (Garden)	0.005	N/A	N/A	0.0054	250	N/A	N/A	**250**
Child 6<11 yrs (Gardens)	0.003	N/A	N/A	0.0030	360	N/A	N/A	**360**

1 Bolded risk estimates should contribute to the residential exposure portion of the aggregate assessment.
2 Residential Handler Dose = the highest handler dose for each applicable lifestage of all residential handler scenarios assessed. Total = dermal + inhalation.
3 Residential Handler MOE = the MOEs associated with the highest residential handler doses. Total = 1 ÷ (1/Dermal MOE) + (1/Inhalation MOE).
4 Residential Post-application Dose = the highest post-application dose for each applicable lifestage of all post-application scenarios assessed. Total = dermal + inhalation + incidental oral.
5 Residential Post-application MOE = the MOEs associated with the highest post-application doses. Total = Dermal MOE + Inhalation MOE + Incidental Oral MOE.

6.1 Residential Bystander Postapplication Inhalation Exposure

Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment was not performed for difenoconazole at this time primarily because of the low acute inhalation toxicity (Toxicity

Category III and IV), low vapor pressure (2.5 x 10^{-10} mm Hg at 25 ºC), and the low proposed use rate (0.13 lb ai/A). However, volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 20101. The Agency is in the process of evaluating the SAP report and may, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are developed, the Agency may revisit the need for a quantitative post-application inhalation exposure assessment for difenoconazole.

6.2 Spray Drift

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for difenoconazole**.** The Agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information). [2] The Agency is also taking means to qualitatively and qualitatively address spray drift as a potential source of exposure in risk assessments for pesticides through existing programs such as Ag Drift and chemical specific properties of pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the *Registration Review* process which ensures that all uses for that pesticide will be considered concurrently.

7.0 AGGREGATE EXPOSURE/RISK CHARACTERIZATION

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures (dermal and residential). In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

7.1 Acute & Chronic Aggregate Risk

Acute and chronic aggregate exposures include food plus drinking water exposures. As demonstrated under Section 5.4, acute and chronic aggregate risks are not of concern.

7.2 Short-Term Aggregate Risk

Short term aggregate exposure takes into account residential exposure plus average exposure levels to food and water (considered to be a background exposure level). The short term aggregate risk includes the estimated risk associated with combined risks from average food and drinking water exposures and dermal and inhalation exposures from adults handling difenoconazole with a backpack sprayer and from post-application exposure to children 6 to 11 years old re-entering a treated garden scenario. Short term aggregate risk estimates are provided in Table 7.2.

1 Available: http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html
2 Available: http://www.epa.gov/opp00001/factsheets/spraydrift.htm

Table 7.2. Short-Term Aggregate Risk Calculations							
Population	Short-Term Scenario						
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day[3]	Total Exposure mg/kg/day[4]	Aggregate MOE (food, water, and residential)[5]
Adult Male	1.25	100	0.0125	0.0021	0.0054	0.0075	170
Adult Female				0.0018	0.0054	0.0072	170
Child				0.0037	0.0030	0.0067	190

[1] 10X for interspecies extrapolation, 10X for intraspecies variation.
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC.
[3] Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]. Refer to Table 6.0.3.
[4] Total Exposure = Avg Food & Water Exposure + Residential Exposure).
[5] Aggregate MOE = [NOAEL/ (Avg Food & Water Exposure + Residential Exposure)].

Updated Aggregate Assessment of Free Triazole & its Conjugates

Reference: *Common Triazole Metabolites: Updated Aggregate Human Health Risk Assessment to Address The New Section 3 Registrations For Use of Propiconazole on Rapeseed Crop Subgroup 20A; Use of Difenoconazole on Rapeseed Crop Subgroup 20A; and Use of Tebuconazole on Imported Oranges. DP414952, T. Morton, 10/24/13.*

The addition of the new proposed uses did not increase the aggregate exposure to free triazoles and its conjugates. Therefore, the previous aggregate human health risk assessment for free triazoles and its conjugates is adequate and the aggregate estimates are below HED's level of concern (DP414952, T. Morton, 10/24/13).

7.3 Intermediate-Term Aggregate Risk

There are no residential use scenarios that will result in potential intermediate term exposure to difenoconazole. Therefore, an intermediate-term aggregate was not performed.

8.0 CUMULATIVE EXPOSURE/RISK CHARACTERIZATION

Difenoconazole is a member of the triazole-containing class of pesticides. Although conazoles act similarly in plants (fungi) by inhibiting ergosterol biosynthesis, there is not necessarily a relationship between their pesticidal activity and their mechanism of toxicity in mammals. Structural similarities do not constitute a common mechanism of toxicity. Evidence is needed to establish that the chemicals operate by the same, or essentially the same, sequence of major biochemical events (EPA, 2002). In conazoles, however, a variable pattern of toxicological responses is found; some are hepatotoxic and hepatocarcinogenic in mice. Some induce thyroid tumors in rats. Some induce developmental, reproductive, and neurological effects in rodents. Furthermore, the conazoles produce a diverse range of biochemical events including altered cholesterol levels, stress responses, and altered DNA methylation. It is not clearly understood whether these biochemical events are directly connected to their toxicological outcomes. Thus, there is currently no evidence to indicate that conazoles share common mechanisms of toxicity and EPA is not following a cumulative risk approach based on a common mechanism of toxicity for the conazoles. For information regarding EPA's procedures for cumulating effects from substances found to have a common mechanism of toxicity, see EPA's website at http://www.epa.gov/pesticides/cumulative.

Difenoconazole is a triazole-derived pesticide. This class of compounds can form the common metabolite 1,2,4-triazole and two triazole conjugates (triazolylalanine and triazolylacetic acid). To support existing tolerances and to establish new tolerances for triazole-derivative pesticides, including propiconazole, U.S. EPA conducted a human health risk assessment for exposure to 1,2,4-triazole, triazolylalanine, and triazolylacetic acid resulting from the use of all current and pending uses of any triazole-derived fungicide. The risk

assessment is a highly conservative, screening-level evaluation in terms of hazards associated with common metabolites (e.g., use of a maximum combination of uncertainty factors) and potential dietary and non-dietary exposures (i.e., high end estimates of both dietary and non-dietary exposures). In addition, the Agency retained the additional 10X FQPA safety factor for the protection of infants and children. The assessment includes evaluations of risks for various subgroups, including those comprised of infants and children. The Agency's complete risk assessment is found in the propiconazole reregistration docket at http://www.regulations.gov, Docket Identification (ID) Number EPA-HQ-OPP-2005-0497.

9.0 OCCUPATIONAL EXPOSURE/RISK CHARACTERIZATION

9.1 Exposure Scenarios

Occupational handler and post-application exposure scenarios have been identified for the proposed uses. Based on the product labels and information provided by the registrant, short- and intermediate-term exposure is expected for occupational handlers and post-application activities. Chronic exposure is not expected for the proposed use patterns.

9.2 Handler Exposure

The term "handler" applies to individuals who mix, load, and apply the pesticide product.
There is a potential for exposure to difenoconazole during mixing, loading, and application activities through the dermal and inhalation routes.

9.2.1 Handler Exposure Scenarios

Occupational handler exposure and risk estimates for the proposed new uses on legume subgroup 6C and bushberry subgroup 13-07B, post-harvest applications on pome fruit 11-10, and vegetable transplants are all expected to result in comparable/identical exposure scenarios previously assessed in recent occupational risk assessments for this chemical (D398608, I. Nieves, 05/30/2012; D412811, I. Nieves, 11/13/2013). The application rates proposed for these new uses are similar to the ones previously assessed (0.11 lb ai/A for legumes and bushberries; $1.35x10^{-6}$ lb ai/ lb fruit for Pome Fruits; and 0.11 for vegetable transplants), and risk estimates were quantified at higher rates, and/or higher amount used or area treated than the proposed uses. No risk estimates of concern were identified to any of the previous uses utilizing label required PPE (i.e., long shirt, long pants, shoes, socks and gloves). Based on the premise that all uses require the same PPE previously labeled, there have been no revisions to the toxicological database/endpoints and/or to the occupational SOPs since the date of the oldest Occupational/Residential Exposure Risk Assessment (2012), all proposed new uses are considered to be not of concern to the Agency.

The proposed use on ornamentals, was previously assessed in 2011 (D371037, B. Daiss, 2/24/11), at a higher application rate than currently proposed (0.003 lb ai/gal vs. 0.0011lbai/gal). However, to reflect recent updates (2012) to HED's occupational exposure SOPs (application methods) and body weight assumptions, this use has been reassessed.

Difenoconazole Exposure Risk Estimates to Ornamentals Summary									
Exposure Scenario	**Crop or Target**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**		**Inhalation**		**Combined MOEs[7]**
		Baseline + Gloves	**No Respirator**		**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[4]**	**MOE[5]**	**LOC=100**
Mixer/Loader/Applicator; Application Rate: 0.0011 lb ai/gal									
Backpack Sprayer – Foliar	Nursery (ornamentals, vegetables, container stock); Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables); Landscaping, Trees/shrubs/bushes, plants/flowers;	11200	140	40 gal	0.00037	3,400	0.000077	16,000	2,800
Backpack Sprayer – Ground Directed	Nursery (ornamentals, vegetables, container stock);	8260	2.58	40 gal	0.00027	4,600	0.0000014	870,000	4,600
Manually Pressurized Handwand – Foliar	Nursery (ornamentals, vegetables, container stock); Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables); Landscaping, Trees/shrubs/bushes, plants/flowers;	430	30	40 gal	0.000014	88,000	0.000017	76,000	41,000
Mechanically Pressurized Handgun – Foliar & Ground Directed	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables);	2500	120	1000 gal	0.0021	610	0.0017	760	340
Mechanically Pressurized Handgun – Foliar & Ground Directed	Nursery (ornamentals, vegetables, container stock); Landscaping, Trees/shrubs/bushes, plants/flowers; Field Crop – typical[6]	390	3.9	1000 gal	0.00032	3,900	0.000054	23,000	3,300

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table"; Level of mitigation: Baseline, PPE, Eng. Controls. Aerial applicators = Eng. Controls, all other estimates are baseline PPE.
2 Based on proposed label (Reg. No. 100-xxxx).
3 Exposure Science Advisory Council Policy #9.1.
4 Dermal/Inhalation Dose = Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (80 kg).
5 Dermal/Inhalation MOE = NOAEL (ST/IT = 1.25 mg/kg/day) ÷ Dose (mg/kg/day).
6 Field Crop Typical = Vegetable Transplants (Brassica, Bulb Vegetables, Cucurbit Vegetables, Fruiting Vegetables
7 Combined MOEs = NOAEL (ST/IT = 1.25 mg/kg/day) ÷ Dermal Dose (mg/kg /day) + Inhalation Dose (mg/kg/day).

9.3 Post-Application Exposure

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

Dermal Exposure

Post-application dermal exposure and risk estimates for the proposed new uses on legume subgroup 6C and bushberry subgroup 13-07B; post-harvest applications on pome fruit 11-10; and on ornamental plants and vegetable transplants grown in both indoor and outdoor production facilities are all expected to result in comparable/identical exposure scenarios to those assessed in previous occupational exposure assessments for this chemical (D398608, I. Nieves, 05/30/2012; D412811, I. Nieves, 11/13/2013). The application rates proposed for these new uses are identical to the ones previously assessed (0.11 lb ai/A for legumes and bushberries; $1.35x10^{-6}$ lb ai/ lb fruit for Pome Fruits; and 0.11 for vegetable transplants). No risk estimates of concern were identified for any of the previous uses. Based on the premise that no new Dislodgeable Foliar Residue studies have been recently submitted, there have been no revisions to the toxicological database/endpoints and/or to the occupational post-application SOPs since the date of the oldest Occupational/Residential Exposure Risk Assessment (2012), all post-applications activities related to the proposed new uses are considered to be not of concern to the Agency.

The post-application potential for dermal exposure of difenoconazole from the proposed use on ornamentals have been re-visited to reflect recent updates (2012) on HEDs Occupational SOPs and body weight assumptions. The following post-application activities have been identified from the proposed use on ornamentals: hand harvesting; hand set irrigation; hand pruning; scouting; container moving; hand weeding; propagating; hand pruning; transplanting; pinching; and tying/training. Hand set irrigation was identified with the highest exposure potential. Table 9.3.1 provides a summary of the anticipated post-application activities and associated transfer coefficients for the proposed crops/use sites.

9.3.1. Anticipated Post-Application Activities and Dermal Transfer Coefficients.

Proposed Crops	Crop Height	Foliage Density	Transfer Coefficients* (cm^2/hr)	Activities
Nursery Crop	High/Low	Full/Min	1,900	Hand Set Irrigation

9.3.1. Anticipated Post-Application Activities and Dermal Transfer Coefficients.				
Proposed Crops	**Crop Height**	**Foliage Density**	**Transfer Coefficients* (cm^2/hr)**	**Activities**
(Ornamentals, Non-bearing Plants)			230	Hand harvesting; hand pruning; scouting; container moving; hand weeding; propagating; hand pruning; transplanting; pinching; tying/training.

*It is the policy of HED to use the best available data to assess post-application exposure. Sources of generic post-application data, used as surrogate data in the absence of chemical-specific data, are derived from ARTF exposure monitoring studies, and, as proprietary data, are subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting post-application exposure that are used in this assessment, known as "transfer coefficients", are presented in the ExpoSAC Policy 3[3]" which, along with additional information about the ARTF data, can be found at the Agency website[4].

No risk estimates of concern were identified for any of the post-application scenarios assuming treated area re-entry immediately after application. Table 9.3.2 presents results for the highest exposure potential scenario (hand set irrigation) at the maximum proposed application rate (0.13 lb ai/A).

Table 9.3.2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Difenoconazole.					
Crop/Site	**Activities**	**Transfer Coefficient (cm^2/hr)**	**DFR[1]**	**Dermal Dose ($mg/kg/day$)[2]**	**MOE[3]**
Short- and Intermediate- term					
Nursery Crop (Ornamentals, Non-bearing Plants)	Hand Set Irrigation	1,900	0.36	0.0042	300

1 DFR = Application Rate × F × $(1\text{-}D)^t$ × 4.54E8 µg/lb × 2.47E-8 $acre/cm^2$; where F = 0.25 and D = 0.10 per day

2 Daily Dermal Dose = [DFR ($\mu g/cm^2$) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day × dermal absorption (%)] ÷ BW (kg).

3 MOE = POD (mg/kg/day) / Daily Dermal Dose.

Inhalation Exposure

Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment was not performed for difenoconazole at this time primarily because of the low acute inhalation toxicity (Toxicity Category III and IV), low vapor pressure (2.5×10^{-10} mm Hg at 25 ºC), and low proposed use rates (highest proposed rate = 0.13 lb ai/A). However, there are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[5]. The Agency is in the process of evaluating the SAP report as well as available post-application inhalation exposure data generated by the ARTF and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation

3 Available: http://www.epa.gov/pesticides/science/exposac_policy3.pdf
4 Available: http://www.epa.gov/pesticides/science/post-app-exposure-data.html
5 Available: http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html

exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for difenoconazole.

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

9.3.1 Restricted Entry Interval

The REI specified on the proposed label is based on the acute toxicity of difenoconazole. Difenoconazole is classified as Toxicity Category III for acute dermal toxicity and eye irriitation, and Toxicity Category IV for skin irritation potential. It is not a skin sensitizer. Short- and intermediate-term post-application risk estimates were not a concern on day 0 (12 hours following application) for all post-application activities. Under 40 CFR 156.208 (c) (2) (iii), active ingredients classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 12 hours on the proposed labels is adequate to protect agricultural workers from post-application exposures to difenoconazole.

10. REFERENCES

Difenoconazole. New Foliar Uses on Pea and Bean, Dried Shelled, Except Soybean, Subgroup 6C and Bushberry

Subgroup 13-07B. Summary of Analytical Chemistry and Residue Data. - B. Cropp-Kohlligian, D418479 and D421194, 10/15/2014

Difenoconazole. Request to Register New Multiple Active Ingredient (MAI) End-Use Product (Academy™ Fungicide) for New Post-Harvest Uses on Pome Fruit Group 11-10. Summary of Analytical Chemistry and Residue Data. - B. Cropp-Kohlligian, D417611, 10/17/2014

Difenoconazole. Acute and Chronic Aggregate Dietary Exposure and Risk Assessments for the Petition for Use of Difenoconazole on Pea and Bean, Dried Shelled, Except Soybean, Subgroup 6C, Bushberry Subgroup 13-07B and an amended use on Pome Fruit to add Post-Harvest Use of Difenoconazole. - T. Morton, D421430, 2/24/15

Drinking Water Exposure Assessment in support of the new use registration of multiple difenoconazole formulated products on Artichoke, Berry Bushberry Subgroup 13-07B, Ginseng, and Bean and Pea, Dried Shelled (except Soybean) Subgroup 6C as well as Conversion of Stone Fruit Crop Group 12-12 and Tree Nuts Crop Group 14-12.. – F. Khan, D421092, 11/13/14

Difenoconazole. Occupational and Residential Exposure Assessment for a Proposed Use on Canola and Oilseed Subgroup 20A. - I. Nieves, D412811, 09/13/2013

Difenoconazole. Occupational and Residential Exposure Assessment to Evaluate the Risk from Proposed Uses on Post-Harvest Potatoes, and the Expansion of Various Crop Groups Including: Citrus Fruit Group 10-10; Fruiting Vegetable Subgroups 8-10; Low Growing Berry Subgroup 13-07G, except cranberry; Pome Fruit, Crop Group 11-10 and Fruiting Vegetable, Crop Group 8-10). - I. Nieves, D398608, 5/30/2012

Difenoconazole. Occupational and Residential Exposure Assessment for the Proposed New Use of Difenoconazole on Strawberry, Carrot, Chickpeas, Soybean, Stone Fruit: Group 12 and Golf Course Turfgrass. - Rebecca Daiss; D371037; February 24, 2011.

Difenoconazole. Occupational and Residential Exposure/Risk Assessment for the Proposed New Uses of Difenoconazole on Fruiting Vegetables, Tuberous and Corm Vegetables, Pome Fruit, Sugar Beets and Ornamentals - Mark I. Dow; D340044; July 27, 2007.

APPENDICES

A TOXICOLOGY DATA SUMMARY

A.1 Guideline Data Requirements - Difenoconazole

Guideline No.	Study Type	Technical		MRID No.
		Required	Submitted	
870.3100	Subchronic (Oral) Toxicity - Rodent	Y	Y	42090022 42090021
870.3150	Subchronic (Oral) Toxicity - Non-Rodent	Y	Y	42090013
870.3200	21/28-Day Dermal Toxicity	N	Y	42090013 46950310
870.3250	90-Day Dermal Toxicity	N	N	
870.3465	90-Day Inhalation Toxicity	N*	N	
870.3700a	Prenatal Developmental Toxicity - Rodent	Y	Y	42090016 42710008
870.3700b	Prenatal Developmental Toxicity - Non-Rodent	Y	Y	42090017 42710008
870.3800	Reproduction and Fertility Effects	Y	Y	42090018
870.4100a	Chronic (Oral) Toxicity - Rodent	Y	Y	42090015 42710006
870.4100b	Chronic (Oral) Toxicity - Non-Rodent (Dog)	Y	Y	42090012 42710005
870.4200a	Carcinogenicity - Rat	Y	Y	42090019 42710010
870.4200b	Carcinogenicity - Mouse	Y	Y	42090015 42710006
870.4300	Combined Chronic Toxicity /Carcinogenicity	Y	Y	42090019, 42710010
870.6100a	Neurotoxicity - Acute Delayed Neurotox.- Hen	N	N	---
870.6100b	Neurotoxicity - Subchronic - Hen	N	N	---
870.6200a	Neurotoxicity - Acute - Rat	Y	Y	46950327
870.6200b	Neurotoxicity -Subchronic - Rat	Y	Y	46950329
870.6300	Developmental Neurotoxicity……	N	N	--
870.7485	General Metabolism	Y	Y	42090028
870.7600	Dermal Penetration	Y	Y	47453201 46950333 47453202 47453203
870.7800	Immunotoxicity……..	Y	Y	48696701

* The Hazard and Science Policy Council (HASPOC) concluded that a 28-day inhalation toxicity study is not required at this time (TXR 0054074).

A.2 Toxicity Profiles

Table A.1. Acute Toxicity Profile – Difenoconazole				
Guideline No.	**Study Type**	**MRID No.**	**Results**	**Toxicity Category**
870.1100	Acute oral	42090006	LD_{50} = 1450 mg/kg	III
870.1200	Acute dermal	42090007	LD_{50} > 2010 mg/kg	III
870.1300	Acute inhalation	42090008	LC_{50} > 3.3 mg/L	III
870.2400	Eye irritation	42090009	Mild irritation reversible in 7 days	III
870.2500	Dermal irritation	40789807	Slight irritation	IV
870.2600	Skin sensitization	42090011, 42710004	Negative	N/A

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	42090022 (1987) **Acceptable/guideline** 0, 20, 200, 750, 1500 or 3000 ppm 0, 1, 10, 37.5, 75 and 150 mg/kg/d	**NOAEL** = 20 ppm (1 mg/kg/day) **LOAEL** = 200 ppm (10 mg/kg/day) based on the 10% decrease in body weight in the 200 ppm females (as well as a negative trend in feed consumption) and Increases in absolute liver weights in both sexes
870.3100	90-Day oral toxicity (mouse)	42090021 (1987) **Acceptable/guideline** 0, 20, 200, 2500, 7500 or 15,000 ppm M: 0, 2.9, 30.8, 383.6, 1125 and 2250 mg/kg/d F: 0, 4.1, 41.5, 558.9, 1125 and 2250 mg/kg/d	**NOAEL** = 20 ppm (2.9 mg/kg/day) **LOAEL** = 200 ppm (30.8 mg/kg/day) based on body weight changes & liver histopathology.
870.3150	26-Week oral toxicity	42090012 (1987) **Acceptable / guideline** 0, 100, 1000, 3000 or 6000 ppm M: 0, 3.6, 31.3, 96.6 and 157.8 mg/kg/d F: 0, 3.4, 34.8, 110.6 and 203.7 mg/kg/d	NOAEL = 3000 ppm (31.3 mg/kg/day in males/34.8 mg/kg/day in females) LOAEL = 6000 ppm (96.6 mg/kg/day in males/110.6 mg/kg/day in females), based primarily on microscopic examination of CGA 169374-related lenticular cataracts.
870.3200	21/28-Day dermal toxicity (rat)	42090013 (1987) **Acceptable / guideline** 0, 10, 100 and 1000 mg/kg/d	**NOAEL** = 10 mg/kg/day **LOAEL** = 100 mg/kg/day based on statistically significant decrements in body weight, body weight gain, and food consumption.
870.3200	21/28-Day dermal toxicity (rat)	46950310 (2000) **Acceptable/ guideline** 0, 10, 100 and 1000 mg/kg/d	**NOAEL** (systemic) = 1000 mg/kg/day **LOAEL** (systemic) was not determined. **NOAEL** (dermal) = 100 mg/kg/day **LOAEL** (dermal) = 1000 mg/kg/day based on hyperkeratosis at the skin application site.

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700a	Prenatal developmental in (rat)	42090016, 42710007 (1987) **Acceptable** / **guideline** 0, 2, 20, 100 or 200 mg/kg/d from GD 6-15 (nominal doses differed widely from theoretical, this required altering NOAEL/LOAEL values)	**Maternal NOAEL** = 16 mg/kg/day **LOAEL** = 85 mg/kg/day based on decreased body weight gain and food consumption. **Developmental NOAEL** = 85 mg/kg/day **LOAEL** = 171 mg/kg/day based on alterations in fetal ossification.
870.3700b	Prenatal developmental in (rabbit)	42090017, 42710008 (1987) **Acceptable** / **guideline** 0, 1, 25 or 75 mg/kg/d from GD 7-19	**Maternal NOAEL** = 25 mg/kg/day **LOAEL** = 75 mg/kg/day based on decreased body weight gain and food consumption. **Developmental NOAEL** = 25 mg/kg/day **LOAEL** = 75 mg/kg/day based on nonsignificant increases in postimplantation loss and resorptions/doe and a significant decrease in fetal weight.
870.3800	Reproduction and fertility effects (rat)	42090018 (1988) **Acceptable** / **guideline** 0, 25, 250 or 2500 ppm 0, 1.25, 12.5 and 125 mg/kg/d	**Parental/Systemic NOAEL** = 25 ppm (1.25 mg/kg/day) **LOAEL** = 250 ppm (12.5 mg/kg/day) based on reductions (statistically nonsignificant) in body weight gain which appear to be part of a dose-related trend days 70-77 prior to mating, days 0-7 of gestation, and days 7-14 of lactation **Offspring NOAEL** = 25 ppm (1.25 mg/kg/day) **LOAEL** = 250 ppm (12.5 mg/kg/day) based on a significant reduction in the body weight of F1 male pups at day 21 in the 250 ppm group.
870.4100b	Chronic toxicity (dog)	42090012, 42710005 (1988) **Acceptable** / **guideline** 0, 20, 100, 500 or 1500 ppm M: 0, 0.71, 3.4, 16.4 and 51.2 mg/kg/d F: 0, 0.63, 3.7, 19.4 and 44.3 mg/kg/d	**NOAEL** = 100 ppm (3.4 mg/kg/day in males/3.7 mg/kg/day in females) **LOAEL** = 500 ppm (16.4 mg/kg/day in males/19.4 mg/kg/day in females), based on significant inhibition of body weight gain in females.
870.4200	Carcinogenicity (rat)	42090019, 42710010 (1989) **Acceptable** / **guideline** 0, 10, 20, 500 or 2500 ppm M: o, 0.48, 0.96, 24.12 and 123.7 mg/kg/d F: 0, 0.64, 1.27, 32.79 and 169.6 mg/kg/d	**NOAEL** = 20 ppm (0.96 mg/kg/day in males/1.27 mg/kg/day in females) **LOAEL** = 500 ppm (24.1 mg/kg/day in males/ 32.8 mg/kg/day in females) based on reductions in cumulative body weight gains in the 500 and 2500 ppm groups. No evidence of carcinogenicity
870.4300	Carcinogenicity (mouse)	42090015, 42710006 (1989) **Acceptable** / **guideline** 0, 10, 30, 300, 2500 or 3000 ppm M: 0, 1.51, 4.65, 46.29, 423.1 and 818.9 mg/kg/d F: 0, 1.9, 5.63, 57.79 and 512.6 mg/kg/d	**NOAEL** = 30 ppm (4.7 mg/kg/day in males/5.6 mg/kg/day in females) **LOAEL** = 300 ppm (46.3 mg/kg/day in males/57.8 mg/kg/day in females) based on reductions in the cumulative body weight gains and hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis in the 300, 2500 & 4500 ppm groups. Evidence of carcinogenicity (liver adenoma/carcinoma in both sexes)

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5100	*In vitro* bacterial gene mutation *(Salmonella typhimurium/ E. coli)*/ mammalian activation gene mutation assay	42090019, 42710010 (1989) **Acceptable** / **guideline** 340 - 5447 µg/plate; 85 - 1362 µg/plate (repeat assay with TA1537 and TA98)	There were sufficient and valid data to conclude that CGA 169374 technical was negative in the microbial gene mutation assay.
870.5300	*in vitro* mammalian cell gene mutation assay in mouse lymphoma cells	42090024 (1986) **Unacceptable/ guideline**	No conclusion can be reached from the three nonactivated and two S9 activated mouse lymphoma forward mutation assays conducted with difenoconazole technical. The study was seriously compromised.
870.5375	*In vitro* Mammalian Cytogenetics (chromosomal aberrations) assay in Chinese hamster CHO cells	46950319 (2001) **Acceptable/ guideline** 0, 21.99, 27.49, or 34.36 µg/mL (-S9) 0, 34.36, 53.69 or 67.11 µg/mL (+S9)	There was evidence of a weak induction of structural chromosomal aberrations over background in the presence of S9-mix.
870.5375	*In vitro* Mammalian Cytogenetics (chromosomal aberrations) assay in Chinese hamster CHO cells	46950321 (2001) **Acceptable/ guideline** 0, 26.3, 39.5 or 59.3 µg/mL (-S9) 0, 11.7 or 17.6 µg/mL (+S9)	There was evidence of a weak induction of structural chromosomal aberrations over background.
870.5375	*In vitro* Mammalian Cytogenetics (chromosomal aberrations) assay in human lymphocytes	46950323 (2001) **Acceptable/ guideline** 0, 5, 30 or 75 µg/mL (-S9) 0, 5, 30 or 62 µg/mL (+S9)	There was no evidence of structural chromosomal aberrations induced over background.
870.5385	*In vivo* mammalian chromosomal aberration test Assay in Mice	42090023 (1986) **Unacceptable/guideline** 250, 500 or 1000 mg/kg	There was no evidence of a cytotoxic effect on the target organ or significant increase in the frequency of nuclear anomalies (micronuclei). However, the study was compromised.
870.5395	*In vivo* mammalian cytogenetics - erythrocyte micronucleus assay in mice	41710011 (1992) **Acceptable/guideline** Doses up to 1600 mg/kg	Mice bone marrow - No increase in micronucleated polychromatic erythrocytes occurred with CGA-1 69374 (91.2% a.i).

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	4210012 (1992) Acceptable/ guideline Doses up to 50 µg/mL	CGA-i69374 tech. (92.2% a.i.) was considered to be negative in the unscheduled DNA synthesis assay in rat primary hepatocytes as measured by an autoradiographic method at concentrations up to 50.0 µg/mL.
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	42090027 (1985) **Unacceptable/ guideline** 0.25-31.25 µg/mL	No conclusion can be reached from the unscheduled DNA synthesis (UDS) primary rat hepatocyte assay conducted with difenoconazole technical at concentrations ranging from 0.25 to 31.25 µg /mL. The sensitivity of the study was severely compromised.
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	42090026 (1985) **Unacceptable/ guideline** 0.08-10 µg/mL	No conclusion can be reached from the unscheduled DNA synthesis (UDS) human fibroblast assay conducted with difenoconazole tech. at conc. ranging from 0.08 to 10 µg /mL.
870.6200a	Acute neurotoxicity screening battery	46950327 (2006) **Acceptable/ guideline** 0, 25, 200 or 2000 mg/kg/d	**NOAEL** (M) = 25 mg/kg/day **LOAEL** (M) = 200 mg/kg/day based on reduced fore-limb grip strength in males on day 1 and increased motor activity on Day 1. **NOAEL** (F) = 200 mg/kg/day **LOAEL** (F) = 2000 mg/kg/day based on decreased body weight, the following clinical signs: upward curvature of the spine, tip-toe gait, decreased activity, piloerection and sides pinched in and decreased motor activity.
870.6200b	Subchronic neurotoxicity screening battery	46950329 (2006) **Acceptable/ guideline** 0, 40, 250, or 1500 ppm M; 0, 2.8, 17.3 or 107.0 mg/kg/d F: 0, 3.2, 19.5, or 120.2 mg/kg/d	**NOAEL** (M) = 40 ppm (2.8 mg/kg/day) **LOAEL** (M) = 250 ppm (17.3 mg/kg/day) based on decreased hind limb strength. **NOAEL** (F) = 250 ppm (19.5 mg/kg/day) **LOAEL** (F) = 1500 (120.2 mg/kg/day) based on decreased body weight, body weight gain and food efficiency.
870.7800	Immunotoxicity [dietary] - Mouse	48696701 (2011) **Acceptable/ guideline** 0, 20, 200, 1000, or 1500 pm (0, 3, 35, 177, or 247 mg/kg/day) for 28 days.	**Systemic toxicity NOAEL** = 200 ppm (35 mg/kg/day) **Systemic toxicity LOAEL** = 1000 ppm (177 mg/kg/day) based on decreased body weight gains and liver toxicity **Immunotoxicity NOAEL** = 200 ppm (35 mg/kg/day) **Immunotoxicity LOAEL** = 1000 ppm (177 mg/kg/day) based on decreased mean anti-SRBC IgM levels.
870.7600 Dermal Penetration	*In vivo* Dermal Penetration in the Rat, *In vitro*	47453201 (2007)	**See TXR 0056473**
870.7600 Dermal Penetration	*In vivo* Dermal Penetration in the Rat,	46950333 (2003)	**See TXR 0056473**

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7600 Dermal Penetration	*In vitro* Absorption through Human Epidermis;	47453202 (2007)	**See TXR 0056473**
870.7600 Dermal Penetration	*In vitro* Absorption through Rat Epidermis;	47453203 (2007)	**See TXR 0056473**
870.7485	Metabolism and pharmacokinetics (rat)	42090028 (1990) **Acceptable/ guideline** 14 daily doses of 0.5 or 300 mg/kg	Male and female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [^{14}C]CGA- 169374, or 0.5 mg/kg unlabeled GGA-169374 by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C)CGA-169374 on day 15. The test compound was labeled with C^{14} at either the phenyl or triazole ring.
870.7485	Metabolism and pharmacokinetics (rat)	42090028 (1990) 42090029 (1987) 42090030 (1987) 42090031 (1988) **Acceptable/ guideline** Single oral dose 0.5 or 300 mg/kg 14 daily doses of 0.5 or 300 mg/kg	Male and female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [^{14}C]CGA- 169374, or 0.5 mg/kg unlabeled GGA-169374 by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C)CGA-169374 on day 15. The test compound was labeled with C^{14} at either the phenyl or triazole ring. [^{14}C] CCA 169374 was rapidly and extensively distributed, metabolized, and excreted in rats for all dosing regimens. The metabolism of difenoconazole appears to be extensive because the metabolites accounted for most of the recovered radioactivity in the excrete. Three major metabolites were identified in the feces (i.e. metabolites A, B, and C). Two of the metabolites were separated into isomers (i.e., Al, A2, B1, and B2). Metabolite C was detected only in the high-dose groups, indicating that metabolism of difenoconazole is dose-related and involves saturation of the metabolic pathway. Free triazole metabolite was detected in the urine of triazole-labeled groups and its byproduct was detected in the liver of phenyl labeled groups only. Other urinary metabolites were not characterized.

870.7485	Metabolism and pharmacokinetics (rat)	42090028 (1990) 42090029 (1987) 42090030 (1987) 42090031 (1988) **Acceptable/ guideline** in conjunction with MRIDs 420710013, 42710014 listed below Single oral dose 0.5 or 300 mg/kg 14 daily doses of 0.5 or 300 mg/kg	The absorption, distribution, metabolism, and excretion of CGA 169374 were studied in groups of male and female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [^{14}C]CGA-169374, or 0.5 mg/kg unlabeled GGA-169374 by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C)CGA-169374 on day 15. The test compound was labeled with C^{14} at either the phenyl or triazole ring. **[^{14}C] CCA 169374 was rapidly and extensively distributed, metabolized, and excreted in rats for all** dosing regimens. The extent of absorption is undetermined pending determination of the extent of biliary excretion. The 4-day recoveries were 97.94-107.75% of the administered dose for all dosing groups. The elimination of radioactivity in the feces (78.06-94.61% of administered dose) and urine (8.48-21.86%) were almost comparable for all oral dose groups, with slightly higher radioactivity found in the feces of the high-dose group than the low-dose groups. This was probably due to biliary excretion, poor absorption or saturation of the metabolic pathway. The radioactivity in the blood peaked at about 24-48 hours. Half-lives of elimination appear to be approximately 20 hours for the low-dose groups and 33-48 hours for the high-dose group. The study results also indicate that difenoconazole and/or its metabolites do not bioaccumulate to an appreciable extent following oral exposure since all the tissues contained negligible levels (< 1%) of radioactivity 7 days post exposure. The metabolism of difenoconazole appears to be extensive because the metabolites accounted for most of the recovered radioactivity in the excrete. Three major metabolites were identified in the feces (i.e. metabolites A, B, and C). Two of the metabolites were separated into isomers (i.e., Al, A2, B1, and B2). Metabolite C was detected only in the high-dose groups, indicating that metabolism of difenoconazole is dose-related and involves saturation of the metabolic pathway. Free triazole metabolite was detected in the urine of triazole-labeled groups and its byproduct was detected in the liver of phenyl labeled groups only. Other urinary metabolites were not characterized. These studies indicate that distribution, metabolism, and elimination of CGA-169374 were not sex related. There was a slight dose difference in the metabolism and elimination of CGA-169374. In phenyl and triazole labeling studies, fecal excretion of radioactivity was higher in the high dose animals compared to the low dose animals, and an additional metabolite was found in the

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
			feces of the high dose animals compared to the low dose animals. There was no major difference in the distribution and excretion of radioactivity with labeling at the phenyl and triazole ring positions, however, there were some different metabolites identified. The studies also showed that administration of 0.5 and 300 mg/kg CGA- 169314 did not induce any treatment related clinical effects.

A.3 Toxicological Endpoints

A.3.1 Acute Population Adjusted Doses (aPAD) – All Populations

Selected Study: Acute Neurotoxicity Study in Rats
MRID 46950327
Dose and Endpoint for Establishing an aPAD: NOAEL is 25 mg/kg/day. LOAEL is 200 mg/kg/day based on reduced fore-limb grip strength in males on day 1.
Uncertainty Factor (UF): 100 This includes 10x for interspecies extrapolation and 10x for intraspecies variation, 1X FQPA SF.
Comments about Study/Endpoint: The selected endpoint is considered appropriate for acute dietary exposure because effects were seen after a single dose. The endpoint is protective of the general population and all subpopulations for effects seen in the acute neurotoxicity study in rats. It is also protective of developmental and maternal effects observed in the rabbit developmental toxicity study at the LOAEL of 75 mg/kg/day and NOAEL of 25 mg/kg/day.

$$\textbf{General Population aPAD} = \frac{\textbf{(NOAEL) 25 mg/kg}}{\textbf{(UF) 100}} = \textbf{0.25 mg/kg}$$

A.3.2 Chronic Population Adjusted Dose (cPAD) – All Populations

Selected Study: Chronic/Oncogenicity Study in Rats
MRID 42090019/20
Dose and Endpoint for Establishing an cPAD: The NOAEL is 0.96 mg/kg/day. The LOAEL is 24.12 mg/kg/day based on cumulative decreases in body weight gains at 24.12 mg/kg/day in males.

$$\textbf{General Population cPAD} = \frac{\textbf{(NOAEL) 0.96 mg/kg/day}}{\textbf{(UF) 100}} = \textbf{0.01 mg/kg/day}$$

Uncertainty Factor (UF): 100: This includes 10X for interspecies extrapolation,10x for intraspecies variation, 1X FQPA SF.

A.3.3 Incidental Oral Exposure (Short-Term)

Selected Study: Two Generation Reproduction Study in Rats
MRID 42090018
Dose and Endpoint for Establishing POD: The NOAEL is 1.25 mg/kg/day based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21, and reductions in body weight gain in F0 females.
Uncertainty Factor (UF): An MOE 100 is required for the short- and intermediate-term scenarios for dermal exposure is based on the conventional uncertainty factor of 100. This includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: There are no residential uses for difenoconazole that would result in incidental oral exposure to children. However, a short term oral exposure endpoint is required for aggregate risk assessment.

A.3.4 Dermal Absorption

A dermal absorption factor (DAF) is applied when dermal exposure endpoints are selected from oral toxicity studies. The dermal factor converts the oral dose to an equivalent dermal dose for the risk assessment. A DAF of 6% was selected for use in risk assessment based on available in vivo dermal absorption studies in rat and in vitro dermal absorption studies conducted with rat and human skin (TXR 0056473).

A.3.5 Dermal Exposure (Short and Intermediate-Term)

Selected Study: Two Generation Reproduction Study in Rats (MRID 42090018)

See Section A.4.3

Dose and Endpoint for Establishing POD: The NOAEL is 1.25 mg/kg/day based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21 and reductions in body weight gain in F0 females.. Dermal absorption is 6%.

Uncertainty Factor (UF): An MOE 100 is required for the short- and intermediate-term scenarios for dermal exposure is based on the conventional uncertainty factor of 100. This includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: Although dermal toxicity studies are available, a POD from an oral study was selected because effects in young animals (decreased pup weight) the primary effect of concern for short, intermediate and long term exposure is not specifically

evaluated in the available dermal toxicity studies that only assess adult animals. The selected endpoint is protective of offspring effects from dermal exposure. A DAF of 6% is applied to the POD for dermal exposure.

A.3.6 Inhalation Exposure (Short- and Intermediate-Term)

Selected Study: Two Generation Reproduction Study in Rats (MRID 42090018)

See Section A.4.3

A.4 EXECUTIVE SUMMARIES FOR SUPPORTING TOXICITY STUDIES

A.4.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity – Rat MRID 42090022

CGA-169374 Technical was administered orally in feed admixtures to six groups of rats of both sexes at 0 ppm, 20 ppm, 200 ppm, 750 ppm, 1500 ppm, and 3000 ppm for 13 weeks. The results of this dietary subchronic evaluation of the toxicity of the test article were generally unremarkable. There was a significant trend for decreased body weights in both sexes, and the 200 ppm female rats showed an approximate 10% decrease in body weight relative to their controls concomitant with decreased food consumption. There was one dose—related effect of the chemical discovered during the histopathology examination, that identified modest diffuse hepatocellular enlargement, vis a vis. increased liver weights, in rats of both sexes at the two highest doses tested. Additionally, although not statistically significant, compared to the other groups there was an increase in the frequency and quantity of ketones in the urine of group 6 males. The presence of elevated ketone levels may be due to gluconeogenesis driven by decreased protein intake from the diet as a result of decreased food intake. The somewhat compromised nutritional status of the rats could possibly and indirectly have promoted the hepatocellular enlargement as well.
It is possible to conclude from this study, that based on approximately 10% decrease in body weight in the 200 ppm females (concomitant with a negative trend for food consumption) and increases in absolute liver weights in both sexes appearing at 750 ppm, the LOAEL is 200 ppm. The NOAEL was 20 ppm.
Core Classification: Minimum

870.3100 90-Day Oral Toxicity – Mouse MRID 42090021

CGA 169374 was offered in feed admixtures to five groups of mice composed of 15 animals/group/sex and 20 mice per sex for controls in dietary concentrations of 20 ppm, 200 ppm, 2500 ppm, 7500 ppm, or 15000 ppm for 13 weeks. Most of the mice fed 7500 ppm or 15,000 ppm test article, groups 5 and 6 respectively, died during the first week on study. There were some CGA 169374-related effects. The statistical analysis of total food consumption and body weight changes over the course of the study showed significantly reduced body weight gain

for paired group 4 (2500 ppm) females and a significant negative trend. Compound—related effects from histologic examination were confined to the liver. Hepatotoxicity in mice that DOS was evidenced by hepatocellular enlargement and necrosis of individual hepatocytes. Those mice that survived to the end of the study showed hepatotoxicity that included hepatocellular enlargement in group 4 animals and group 3 males and hepatocytic vacuolization in group 4 animals. Furthermore, coagulative necrosis was observed in the livers of 4/9 group 4 females. This finding, however, was not considered treatment related, because the foci were frequently small and random. The animals in groups 5 and 6, which represent the unscheduled deaths, had a high incidence of changes consistent with stress. The changes included lymphoid depletion or necrosis of the spleen, lymph nodes, and thymus, hypocellularity of the femoral marrow, mucosal erosion/ulceration of the glandular stomach, and in the female mice necrosis of individual cells in the adrenal cortex, specifically in the zona reticularis. Hyperkeratosis of the nonglandular stomach was observed in males especially from group 6. The study director suggests the "stress" effects may be related to inappetence and a failure to eat as opposed to a direct effect of the test article. On the strength of the available data as they relate to the dose levels tested and to the parameters observed, the body weight changes and the liver histopathology form the basis for setting the NOAEL at 20 ppm, and the LOAEL at 200 ppm. The mortality data indicate the MTD was exceeded and is likely S 7500 ppm.

870.3150 26 Week Oral Feeding study –dog OPPTS MRID 42090012

CGA 169374 was offered in feed admixtures to five groups of beagle dogs composed of three animals/group/sex in dietary concentrations of 0 ppm, 100 ppm, 1000 ppm, 3000 ppm, or 6000 ppm for a minimum of 28 weeks. None of the dogs DOS. Compound— related effects, developed essentially at the 3000 ppm and 6000 ppm dose levels. The singularly most striking compound effect was bilateral lenticular cataracts ophthalmoscopically-observed in all dogs at 6000 ppm and in one female beagle at 3000 ppm. Additionally, iridic changes (irregular pupillary margins, miosis), secondary to lens induced uveitis, were also present in the affected animals. There were also reductions in mean body weight in females and males at 6000 ppm test compound throughout the study; weight loss was observed during the first three weeks on study. Body weight loss was precipitated by moderate to severe reductions in mean food consumption in females and males at 6000 ppm during the study with slight reductions observed in males at 3000 ppm and 1000 ppm and in one female at 3000 ppm. Furthermore, there were slight reductions in values for red blood cell count, hemoglobin, and hematocrit in females and males at 6000 ppm. There were also decrements in some serum clinical chemistry measurements including calcium and total protein in females at 6000 ppm and moderate increases in serum alkaline phosphatase in one or both sexes at 3000 ppm. There were modest alterations in several absolute and/or relative organ weight measurements to include the heart, prostate gland, salivary gland, uterus, kidney, liver, and brain at the highest dose tested (HOT). Nevertheless, liver weight measurements were also increased in Group 4 females. There were no other test article—related changes in any other parameter examined. On the strength of the available data as they relate to the dose levels tested and the parameters observed, the LOAEL and the NOAEL for the test article in female and male beagle dogs were 3000 ppm and 1000 ppm, respectively, based primarily on microscopic examination of CGA 169374-related lenticular cataracts. Core

Classification: Minimum

A.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat MRID 42090016

CGA 169347 technical was administered by gavage on days 6-15 of gestation to presumed pregnant rats at 0, 2, 20, 100, or 20a mg/kg. Significant decreases in maternal body weight gain and feed consumption were observed during the dosing period for the feed consumption were observed during the dosing period for the 100 and 200 mg/kg groups. These animals also exhibited a significant increase in the incidence of excess salivation. There was a non-significant decrease in the mean number of fetuses per dam, and non-significant increases in the mean number of resorptions per dam and % postimplantation loss in the 200 mg/kg group. There was a slight (non-significant) decrease in mean fetal body weight at the 200 mg/kg group. The following represents the significant alterations in the development of fetuses in the 200 mg/kg group. The incidence of bifid or unilateral ossification of the thoracic vertebrae was significantly increased on the fetal basis. There were also significant increases in the average number of ossified hyoid and decreases in the average number of sternal centers of ossification (per fetus per litter). The average number of ribs was significantly increased (with accompanying increases in the number of thoracic vertebrae), and decreases in the number of lumbar vertebrae in this group. These findings may be related to maternal toxicity. This study may be upgraded after satisfactory review of the response to the noted deficiencies.
core classification: supplementary. NOTE: Due to the relatively high percent deviation of the actual doses tested from the theoretical concentration the effect levels have been modified accordingly. This modification may be subject to change as the purity is currently unknown.
Maternal NOAEL = 16 mg/kg; Maternal LOEL = 85 mg/kg; Developmental Toxicity NOAEL = 85 mg/kg; Developmental Toxicity LOAEL = 171 mg/kg

870.3700b Prenatal Developmental Toxicity Study – Rabbit MRID 42090017

CGA 169347 technical was administered by gavage on days 7—19 of gestation to presumed pregnant rabbits at 0, 1, 25, or 73 mg/kg. Maternal toxicity was observed in this study as the death of one doe and abortions observed in two other high dose does. In addition, significant reductions in body weight gain of high dose does, were present days 7-10, 10—14, 7-20, and 0—29. These reductions correspond with reduced feed consumption during these intervals (significant reductions in feed consumption in the HDT were only observed during the treatment period, not after treatment). Slight non-significant increases in postimplantation loss and resorptions/doe were observed in the HDT. The significant decrease in fetal weight at the HDT may have been due to treatment. The significant differences in fetal weight observed at the low and mid dose were apparently not due to treatment.
Core Classification: supplementary
Maternal NOAEL = 25 mg/kg; Maternal LOEL = 75 mg/kg
Developmental Toxicity NOAEL 25 mg/kg; Developmental Toxicity LOEL = 75 mg/kg

A.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat MRID 42090018

In a two generation reproduction study, difenoconazole was administered in the diet to male and female rats at 0, 25, 250, or 2500 ppm [0, 1.25, 12.5, or 125 mg/kg/day, respectively]. Statistically significant reductions in body weight gains of F0 and F1 males were observed at 2500 ppm during Days 70-77 and during the course of the study [terminal body weight minus Day 0 body weight]. Significant reductions in body weight gains of F0 and F1 females were seen during the pre-mating, gestation, and lactation periods. A dose-related, but non-statistically significant decreases in body weight gain was seen in F0 females at 250 ppm during Days 70-77 prior to mating, Days 0-7 of gestation, and Days 7-14 of lactation:
At 2500 ppm, significant reductions in pup body weight were detected on Days 0, 4 [pre- and post culling], 7, 14, and 21 for males and females of both generations. There was a significant reduction in the body weight of F1 male pups on Day 21 in the 250 ppm group. The percentage of male pups in the F1 generation surviving Days 0-4 was significantly reduced in the 2500 ppm group: For parental toxicity, the LOAEL of 250 ppm [12.5 mg/kg/day is based on the decreased maternal body weight gain; the NOAEL is 25 ppm [1.25 mg/kg/day. For offspring toxicity, the LOAEL of 250 ppm [12.5 mg/kg/day] is based on decreased pup weights at Day 21; the NOAEL is 25 ppm [1.25 mg/kg/day].

A.4.4 Chronic Toxicity

870.4100a (870.4300) Combined Chronic Toxicity/Carcinogenicity – Rat MRIDs 42090019/ -20

CGA 169374 was administered in the diet to male and female rats [80/sex/dose] for 104 weeks at 0; 10; 20; 500; and 2500 ppm. There were reductions in cumulative body weight gains in the 500 and the 2500 ppm groups. Mean liver weight was increased at week 53 and t termination in the 2500 ppm group. Hepatocellular hypertrophy was observed in the 500 and the 2500 ppm animals at termination. Additional findings in the clinical chemistry data also indicated that liver was the primary target organ for toxicity. No treatment related increased incidences of neoplastic findings were observed in this study. The NOAEL for the study was 20 ppm which was equal to 0.96 and 127 mg/kg/d for males and females respectively. The LOAEL was 500 ppm equal to 24.12 and 32.79mg/kg/day for males and females respectively based on cumulative decreases in body weight gains. Discussion of Tumor Data No treatment related increased incidences of neoplastic findings were observed in this study. Adequacy of the Dose Levels Tested The dose levels tested were considered adequate by the Cancer Peer Review Committee. (memorandum of July 27,1994 from B. Rinde of the Health Effects Division)

870.4100b Chronic Toxicity - Dog MRID 42090012

CGA 169347 was administered in the diet to male and female dogs at 0, 20, 100, 500, or 1500 ppm. The NOAEL was 100 ppm and the LOAEL was

500 ppm based on the following. Females receiving 1500 ppm in the diet had a significant reduction in body weight gain on day 7. Females in the 500 and 1500 ppm groups, although not statistically significant, had inhibited body weight gain throughout the study. These animals also had significant reductions in food consumption on days 7, 35, 70, and 357. The reduction in mean percent reticulocytes at the highest dose tested on day 359 may have been related to treatment, Significant increases (treatment related at day 85; dose—related at days 175 and 359) were observed in alkaline phosphatase in males receiving 1500 ppm. This study may be upgraded upon satisfactory review of the registrants response to the deficiencies (submission of the purity and raw daily observation data).
Classification: core—supplementary

A.4.5 Carcinogenicity

870.4200a Carcinogenicity/Chronic Study – Mice MRIDs 42090015 and 42710006

CD-I mice were fed diets containing difenoconazole at 0; 10; 30; 300; 2500or 4500 [males only] for 78 weeks. The NOAEL was 30 ppm equal to 4.65 mg/kg/d in males and 5.63mg/kg/d in females respectively. The LOAEL was 300 ppm equal to 46.29 mg/kg/d in males and 57.79mg/kg/d in females based on reductions in the cumulative body weight gains at the higher dose levels.

Discussion of Tumor Data: Difenoconazole was reviewed by the HED-CPRC on May 18, 1994 (memorandum of July 27, 1994 from E. Rinde of the HED CPRC to C. Giles-Parker of RD) and classified as a Category C carcinogen without a q-star. The margin-of-exposure (MOE) approach was selected because there was only very weak (limited) evidence of carcinogenic potential at dose levels not considered to be excessive with significant changes observed only at excessive doses. There was no evidence for genotoxicity. There was a statistically significant increase in liver adenomas, carcinomas, and combined liver adenomas and carcinomas in both sexes at doses of 2500 and 4500 ppm. These doses were considered to be excessively high for cancer testing. Liver necrosis and liver adenomas were also noted in males at 300 ppm. There were no statistically significant increases in liver tumors at 10 or 30 ppm. Adequacy of the Dose Levels Tested: The Health Effects Division Cancer Peer Review Committee considered the doses adequate and the study acceptable.

870.4200b Carcinogenicity (feeding) – Rat MRIDs 42090019/ -20

CGA 169374 was administered in the diet to male and female rats [80/sex/dose] for 104 weeks at 0; 10; 20; 500; and 2500 ppm. There were reductions in cumulative body weight gains in the 500 and the 2500 ppm groups. Mean liver weight was increased at week 53 and t termination in the 2500 ppm group . Hepatocellular hypertrophy was observed in the 500 and the 2500 ppm animals at termination. Additional findings in the clinical chemistry data also indicated that liver was the primary target organ for toxicity. No treatment related increased incidences of neoplastic

findings were observed in this study. The NOAEL for the study was 20 ppm which was equal to 0.96 and 127 mg/kg/d for males and females respectively. The LOAEL was 500 ppm equal to 24.12 and 32.79 mg/kg/day for males and females respectively based on cumulative decreases in body weight gains. Discussion of Tumor Data No treatment related increased incidences of neoplastic findings were observed in this study. Adequacy of the Dose Levels Tested The dose levels tested were considered adequate by the Cancer Peer Review Committee. (memorandum of July 27,1994 from B. Rinde of the Health Effects Division)

A.4.6 Mutagenicity

Gene Mutation

Guideline # 870.5100 Bacterial assay 42090019, 42710010 Minimum/ guideline	Not mutagenic
Guideline #870.5300, In vitro mammalian cell gene mutation test MRID 42090024 Unacceptable Guideline	No conclusion can be reached from the three non-activated and two S9 activated mouse lymphoma forward mutation assays conducted with difenoconazole technical. The study was seriously compromised.

Cytogenetics

Guideline # 870.5375, Clastogenicity in mammalian cells MRID 46950319, 46950321 Acceptable Guideline MRID 46950323 Guideline #870.5395 Micronucleus test in bone marrow MRID 41710011 Acceptable Guideline Guideline #870.5550 Unscheduled DNA Synthesis in Mammalian Cells in Culture 4210012 (1992) Acceptable/ guideline	There was evidence of a weak induction of structural chromosomal aberrations over background in the presence of S9-mix. There was no evidence of structural chromosomal aberrations induced over background. Mice bone marrow - No increase in micronucleated polychromatic erythrocytes occurred with CGA-169374 (91.2% a.i). CGA-169374 tech. (92.2% a.i.) was considered to be negative in the unscheduled DNA synthesis assay in rat primary hepatocytes as measured by an autoradiographic method at concentrations up to 50.0 µg/mL.

A.4.7 Neurotoxicity

870.6100 Delayed Neurotoxicity Study – Hen - NA

870.6200 Acute Neurotoxicity Screening Battery – Rat MRID 46950327

In an acute neurotoxicity study (MRID 46950327), groups of fasted Alpk:APfSD Wistar-derived rats (10/sex/dose), at least 42 days old, were given a single oral dose of difenoconazole technical (CGA169374) (94.3% w/w, batch/lot # WM806228) in 1% w/v aqueous carboxymethylcellulose (CMC) at doses of 0, 25, 200, or 2000 mg/kg bw and observed for 14 days. Dose levels selected for this study were based on the results of preliminary acute neurotoxicity study (MRID 46950325). Neurobehavioral assessment (functional observational battery and motor activity testing) was performed on 10 animals/sex/group on days -7, 1, 8, and 15. Body weight and food consumption were measured weekly throughout the study. At study termination, 5 animals/sex/group were euthanized and perfused in situ for neuropathological examination; brain weight was recorded from these animals. Of the perfused animals, 5 animals/sex from the control and high dose groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

There were no unscheduled deaths at any dose level. Weight change on the day of dosing by the control, low-, mid-, and high-dose groups was -2.1, - 1.0, -7.8, and -18.3 g, respectively, for males and 0.0, 2.1, -3.8, and -13.0 g, respectively, for females. Body weight for females had recovered to control levels by day 8. Food consumption for males given 2000 mg/kg was approximately 20% less than control during week 1 only ($p<0.01$). Food consumption for these

animals recovered to control levels during week 2. There were no differences from control for females at any dose level or for males at the lower dose levels. These effects on body weight and food consumption were not toxicologically significant.

At 2000 mg/kg, a number of adverse clinical signs were observed on day I (at the time of **peak** effect), including: upward curvature of the spine (8 males, 9 females); tip-toe gait (3, 8); decreased activity (6, 7); piloerection (3, 5); sides pinched in (3, 7); and subdued (1, 0). Females were affected more than males. All treatment-related clinical signs observed on day 1 showed complete recovery by day 5 (males) or day 7 (females).
Significant decreases in fore-limb grip strength were seen in mid- (23%) and high-dose (26%) males on day 1. Females dosed with 2000 mg/kg had lower motor activities on day 1 (37%), at the time of peak effect, and on day 8 (31%). Males dosed with 200 or 2000 mg/kg had higher motor activities than the controls on day 1, 50% and 55%, respectively, at the time of peak effect. There were no effects on brain weight at any dose level. Neuropathological examination of the central and peripheral nervous system showed no effects of treatment at doses of 2000 mg/kg in both sexes. The LOAEL for acute neurotoxicity of difenoconazole technical (CGA169374) in male rats is 200 mg/kg bw based on reduced fore-limb grip strength in males on day 1. The NOAEL is 25 mg/kg bw. The LOAEL for acute neurotoxicity of difenoconazole technical (CGA169374) in female rats is 2000 mg/kg. Based on decreased body weight, the following clinical signs: upward curvature of the spine, tip-toe gait, decreased activity, piloerection and sides pinched in, and decreased motor activity. The NOAEL is 200 mg/kg bw.

870.6200 Subchronic Neurotoxicity Screening Battery

In a subchronic neurotoxicity study (MRID 46950329) difenoconazole technical (94.5% w/w, batch no. WM806228) was administered to groups of 12 male and 12 female Alpk:AP$_f$SD (Wistar-derived) rats at concentrations of 0, 40, 250, or 1500 ppm in the diet for 90 days. Respective dose levels corresponded to 0, 2.8, 17.3 or 107.0 mg/kg bw/day for males and 0, 3.2, 19.5, or 120.2 mg/kg bw/day for females. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 12 animals/sex/group pretest and during weeks 2, 5, 9, and 14. Cholinesterase activity was not determined. At study termination, 5 animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Of the perfused animals, 5/sex from the control group and 5/sex from the 1500 ppm group were subjected to histopathological evaluation of brain and peripheral nervous system tissues. Treatment with difenoconazole at concentrations up to 1500 ppm in the diet had no effect on mortality or clinical signs. Relative to respective control weight, final body weight of males and females in the 1500 ppm group was reduced by 9% and 7%. Body weight gain was reduced by 22% in males and 23% in females. Food consumption was reduced in this group (statistically significant only in females [7%]), and food efficiency was significantly reduced in males by 21% ($p \leq 0.05$) and in females by 21% (ns). Lower dose groups were unaffected. Absolute liver weight in males and females in the 1500 ppm group was increased over respective control weight by 38% and 45%. Liver was not weighed in lower dose groups. The increase in liver weight was considered a normal response to chemical treatment.

During weeks 2, 9 and 14, hind-limb grip strength in males in the 1500 ppm group was reduced by 18 to 27% relative to the control values. At week 14, hind-limb grip strength in males in the 250 ppm group was significantly ($p \leq 0.05$) reduced by 20% relative to the control values. FOB observations in females were unaffected by treatment. Motor activity was unaffected in both sexes at all observation times. Brain weight was unaffected by treatment and there were no treatment-related neuropathological lesions.

The LOAEL in male rats is 250 ppm in the diet (17.3 mg/kg bw/day), based on decreased hind limb strength. The NOAEL is 40 ppm (2.8 mg/kg bw/day). The LOAEL in female rats is 1500 ppm in the diet (120.2 mg/kg bw/day), based on decreased body weight, body weight gain and food efficiency. The NOAEL is 250 ppm (19.5 mg/kg bw/day). The study is classified as Acceptable/Guideline

A.4.8 Metabolism

870.7485 Metabolism – Rat

Study 1

The absorption, distribution, metabolism, and excretion of difenoconazole were studied in groups of male and, female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [^{14}C] difenoconazole or 0.5 mg/kg unlabeled difenoconazole by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C] difenoconazole on day 15. The test compound was labeled with [^{14}C] at either the phenyl or triazole ring.

[^{14}C] CCA 169374 was rapidly and extensively distributed, metabolized, and excreted in rats for all dosing regimens. the extent of absorption is undetermined pending determination of the extent of biliary excretion. The 4-day recoveries were 97.94-107.75% of the administered dose for all dosing groups. The elimination of radioactivity in the feces (78.06-94.61% of administered dose) and urine (8.48-21.86%) were almost comparable for all oral dose groups, with slightly higher radioactivity found in the feces of the high-dose group than the low-dose groups. This was probably due to biliary excretion, poor absorption or saturation of the metabolic pathway. The radioactivity in the blood peaked at about 24-48 hours for an dosing group. Half-lives of elimination appear to be approximately 20 hours for the low-dose groups and 33-48 hours for the high-dose group. The study results also indicate that difenoconazole and/or its metabolites do not bioaccumulate to an appreciable extent following oral exposure since all the tissues contained negligible levels (< 1%) of radioactivity 7 days post exposure.

The metabolism of difenoconazole appears to be extensive because the metabolites accounted for most of the recovered radioactivity in the excreta. Three major metabolites were identified in the feces (i.e. metabolites A, B, and C). Two of the metabolites were separated into isomers (i.e., Al, A2, B1, and B2). Metabolite C was detected only in the high-dose groups, indicating that metabolism of difenoconazole is dose-related and involves saturation of the metabolic pathway. Free triazole metabolite was detected in the urine of triazole-labeled groups and its byproduct

was detected in the liver of phenyl labeled groups only. Other urinary metabolites were not characterized.

These study results indicate that distribution, metabolism, and elimination of difenoconazole were not sex related. There was a slight dose-related difference in the metabolism and elimination difenoconazole. In phenyl- and triazole-labeling studies, fecal excretion of radioactivity was higher in the high-dose animals compared to the low-dose animals, and an additional metabolite was found in the feces of the high-dose animals compared to the low-dose animals. There were no major differences in the distribution and excretion of radioactivity with labeling at the phenyl and triazole ring positions, however, there were some different metabolites identified. The studies also showed that administration of 0.5 and 100 mg/kg difenoconazole did not induce any apparent treatment-related clinical effects.

The study is classified as acceptable guideline when considered together with data provided in additional rat metabolism studies (MRIDs 42710014, 42710013) submitted as supplemental to this study. This study may be upgraded if the following additional information is provided and is judged to be acceptable:

Study 2

These studies (MRIDs 42710014, 42710013) were submitted because EPA requested additional information not provided in the Sponsor's previously submitted metabolism studies (MRID Nos. 420900-28/29/30/31). The present studies describe the absorption, distribution, and excretion, as well as pharmacokinetics, of [^{14}C] difenoconazole after a single oral gavage dose of 0.5 or 300 mg/kg in rats (Report 1) and isolated and identified urinary metabolites in three females after a single oral gavage dose of 300 mg/kg (Report 2).

Following oral administration of 0.5 or 300 mg/kg ^{14}C-CCA 169374 in rats, the test compound was adequately absorbed and mainly eliminated via the bile; no evidence of bioaccumulation in any tissue was noted. After 48 hours, total recovery (independent of dose and sex) was ≈ 96% of the administered dose. Biliary excretion constituted the main route of elimination with some dose- and sex-dependency (≈ 75% at the low dose for both sexes; 56% for males and 39% for females at the high dose). Urinary and fecal eliminations exhibited a dose-related pattern at 48 hours. In the urine, 9-l4% was eliminated at the low dose versus 1% in the high-dose rats. In the feces, 2-4% was eliminated at the low dose versus 17-22% at the high dose. In cannulated males after 48 hours, ≈ 80% was eliminated via the bile, while ≈ 4% and ≈ 14% were eliminated via urine and feces, respectively. Therefore, this study indicates that most of the dose following oral administration is absorbed as indicated by the biliary excretion data. The dose-related difference in elimination suggests that saturation is reached at the higher dose level resulting in an increase of unabsorbed test material.

Maximum concentration in blood was reached within 2 hours at the low dose and 4 hours at the high dose. By 24 hours, <0.05 ppm equivalent was detected in the blood. Total recovery ranged from 95% to 97% after 48 hours, irrespective of dose and sex. During the first 12 hours, slight differences were evident between males and females with regard to Tmax, Cmax, and rate of

elimination. The concentration in females was approximately half of that in males and was eliminated faster than in males. Mean half-lives in males and females from Tmax to 12 hours, were 6.2 and 4.4 hours, respectively; from 24 to 168 hours, they were 2.8 and 3.7 days, respectively.

Following administration of 300 mg/kg of (^{14}C-phenyl) CGA 169374, 3 major urinary metabolites were identified: sulfate conjugates (and their isomers) of HO-CGA 205375, isomers of HO-CGA 205375, and the hydroxyacetic metabolite of H0-CGA 205373. The major urinary metabolites of CGA 169374 have been identified and no single unknown metabolite accounted for >1.1% of the dose.

These studies alone do not meet the minimum requirements for Guidelines 85-1. However, these studies combined with previously submitted studies (MRID Nos. 420900-28/29/30/31) are considered to be acceptable,

A.4.9 Immunotoxicity

870.7800 Immunotoxicity – Rat

In an immunotoxicity study (MRID 48696701), difenoconazole (97.4% a.i., Batch # SMO4H493) was administered to female Crl:CD-1 (ICR) mice (10/dose) in the diet at concentrations of 0, 20, 200, 1000, or 1500 pm (equivalent to doses of 0, 3, 35, 177, or 247 mg/kg body weight (bw)/day, respectively) for 28 days. Animals in the positive control group received cyclophosphamide at a dose of 10 mg/kg bw/day by oral gavage for 28 consecutive days. On Day 25, animals in all groups were immunized with a suspension of sheep red blood cells (SRBC) by intravenous injection ($2x10^8$ SRBC/animal, 0.25 mL/animal dose volume). On Day 29 the animals were sacrificed and blood was collected. All animals were evaluated for mortality, clinical signs, body weight changes, and food and water consumption. Gross pathology and spleen, thymus, and liver weights were evaluated at necropsy. Histopathology was performed on the liver and spleen of the vehicle control and treatment groups. Immunotoxicity was assessed for all animals by an enzyme-linked immunosorbent assay (ELISA) that measured the concentrations of serum anti-SRBC IgM.

There were no treatment-related effects on mortality, clinical signs, food and water consumption, or spleen and thymus weights. Decreased body weight gains over the course of the study were observed at 1000 and 1500 ppm (-25% and –36%, respectively); the differences did not reach statistical significance. Statistically significant increases in mean absolute and adjusted liver weights were seen at 1000 ppm (+39% and +43%, respectively) and 1500 ppm (+54% for both). Hepatocyte vacuolation, centrilobular hepatocyte hypertrophy, and increased incidences of pale-colored liver and prominent lobulation of the liver were noted in the 1000 and 1500 ppm groups

The systemic toxicity LOAEL for difenoconazole in female mice is 1000 ppm (equivalent to 177 mg/kg bw/day) based on decreased body weight gains and liver toxicity. The NOAEL for systemic toxicity is 200 ppm (equivalent to 35 mg/kg bw/day).

For immunotoxicity, decreased anti-SRBC IgM levels were found at 1000 and 1500 ppm (-36% and -51%, respectively) as measured by an ELISA, reaching statistical significance at 1500 ppm. There were no treatment-related effects on thymus and spleen weights and macropathology or on spleen histopathology. High inter-individual variability in anti-SRBC antibody levels was noted in all the treatment groups as well as in the control group. However, evaluation of individual animal showed that 40% of the animals in the 1000 ppm group and 50% of the animals in the 1500 ppm group had values that were below the range of the control group. The positive control group showed a statistically significant reduction in the anti-SRBC IgM response, confirming the validity of the immunotoxicity assay.

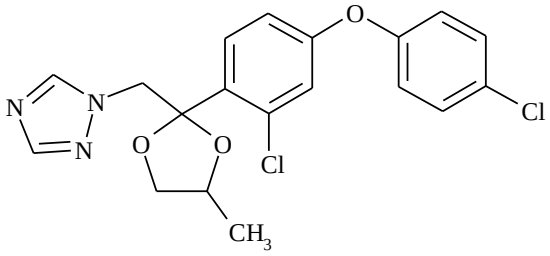
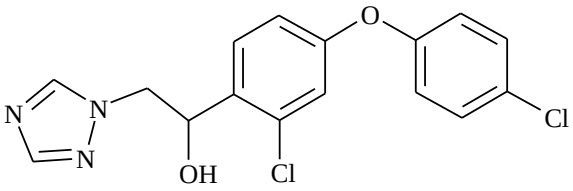
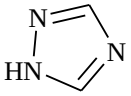
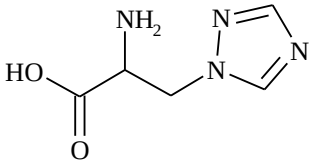
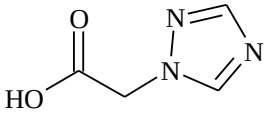
A natural killer (NK) cell activity assay was not performed in this study. The HED guidance stated that if the test substance produces dose-related suppression of the TDAR (anti-SRBC response), then the test substance is considered as immunotoxic and no further study is required. A NK cell activity assay is not required at this time.

Under the conditions of this study, the LOAEL for immunotoxicity is 1000 ppm (equivalent to 177 mg/kg bw/day) based on decreased mean anti-SRBC IgM levels. The NOAEL for immunotoxicity is 200 ppm (equivalent to 35 mg/kg bw/day).

This immunotoxicity study is classified **acceptable/guideline** and satisfies the guideline requirement for an immunotoxicity study (OPPTS 870.7800) in the mouse.

APPENDIX B. Chemical Names And Structures Of Metabolites

B.1 Chemical Names And Structures

Difenoconazole Nomenclature.	
Chemical structure	
Common name	Difenoconazole
Company experimental name	CGA-169374
IUPAC name	1-({2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl}methyl)-1H-1,2,4-triazole
CAS name	1-[[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole
CAS registry number	119446-68-3
Chemical structure of CGA-205375 livestock metabolite	
Chemical structure of 1,2,4-Triazole (1,2,4-T)	
Chemical structure of Triazolylalanine (TA)	
Chemical structure of Triazolylacetic acid (TAA)	

APPENDIX C. Physical/Chemical Properties

Physicochemical Properties of Difenoconazole.		
Parameter	Value	Reference
Melting point	78.6 ºC	DP#s 172067 and 178394, 10/26/92, R. Lascola
pH	6-8 at 20 ºC (saturated solution)	
Density	1.37 g/cm^3 at 20 ºC	
Water solubility	3.3 ppm at 20 ºC	
Solvent solubility	g/100 mL at 25 ºC: n-hexane: 0.5 1-octanol: 35 toluene: 77 acetone: 88 ethanol: 89	
Vapor pressure	2.5 x 10^{-10} mm Hg at 25 ºC	
Dissociation constant, pK_a	pure grade (99.3% ± 0.3%) difenoconazole in water (with 4% methanol) at 20ºC is 1.1	DP# 375159, 5/26/10, B. Cropp-Kohlligian
Octanol/water partition coefficient, Log(K_{OW})	4.2 at 25 ºC	DP#s 172067 and 178394, 10/26/92, R. Lascola
UV/visible absorption spectrum	λ_{max} at about 200 and 238 nm (in methanol at 26 ºC)	PMRA Proposed Regulatory Decision Document on Difenoconazole, 4/14/99 (PRDD99-01)

APPENDIX D. Studies Reviewed for Ethical Conduct

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies were determined to require a review of their ethical conduct, have received that review and have been determined to be ethical.

The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 1995.

The Agricultural Handler Exposure Task Force (AHETF), 2011. The Occupational Handler Unit Exposure Surrogate Reference Table. U.S. Environmental Protection Agency. Released June 21, 2011.

Klonne, D. (1999) Integrated Report for Evaluation of Potential Exposures to Homeowners and Professional Lawn Care Operators Mixing, Loading, and Applying Granular and Liquid Pesticides to Residential Lawns: Lab Project Number: OMA005: OMA001: OMA002. Unpublished study prepared by Riceerca, Inc., and Morse Laboratories. 2213 p. (MRID 44972201).

The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 199